

|CURIEUX|

ACADEMIC JOURNAL

November Issue

Issue 9

Editing Staff

Chief-In-Editor

Caroline Xue

Assisting Editors:

Anshal Vyas

George Hasnah

Olivia Li

Luzia Thomas

Madalyn Ramirez

Shefali Awasthi

Anshal Vyas

Soumya Rai

Sarah Strick

Soumya Rai

Table of Contents

Page 4: Pygmalion Literature Review An Analysis of the Characterization of *Pygmalion* by Andra Fofuca, Blyth Academy Ottawa

Page 10: Democracy and the Tibetan Exile Community A Critique of the Unique Features of the Charter of Tibetans-in-Exile by Ahaan H. Chhatwal

Page 30: The Role of Plant Hormones (Salicylic acid and Jasmonic acid) in Shaping the Plant Root Microbiome by Juezi Huang

Page 44: From England to Vietnam: Tragic Love Stories Across Cultures by Ha Duong

Page 55: Theory X and Theory Y: McGregor's Theories of Management Applied to Working from Home in the Era of COVID-19 by Daniel Youssef

Page 65: The Future of Youth Voter Participation: A Call for States to Revamp Voter Registration Methods by Charlie Selbin

Page 75: Justice in Fyodor Dostoevsky's *The Brothers Karamazov*: The Selfish vs. The Religious by Rosalinda Zhao

Page 87: A Snapshot of Several Major Cytokines in Multiple Sclerosis by Rishi Gadikota

Page 101: The Electric Eel. A Novel Line of Thought? by Avyakta Voruganti

Page 106: Strategies of Functionalizing CB[n] and Their Applications by Shangheng Zhong

Pygmalion Literature Review- An Analysis of the Characterization of *Pygmalion* by George Bernard Shaw by Andra Fofuca, Blyth Academy Ottawa

Introduction

Pygmalion is a play written by George Bernard Shaw, an Irish playwright, which was first performed on stage in the year 1913. It presents a discrete commentary on social classes and prepositions of character, exhibited by a selection of vibrant characters with different contrasts and struggles. Following a failure in fiction, Shaw became a literary critic prior to being a dramatist. Shaw became known for his socialist political views, though they are not necessarily transferred into his work; though *Pygmalion* is a piece surrounding the English social structure at the time, he does not incorporate his political views into the play (Weintraub 1). Shaw's plays are studied to this day in several places to this day, especially in Ireland, showing his influence on modern literature. *Pygmalion*, perhaps the most influential of his pieces, follows two primary characters of opposite social classes, in a story about the power and influence of society.

Synopsis

The first act begins with two men conversing at Covent Garden, the first being Professor Higgins, a stern expert in phonetics, with Colonel Pickering, a formal and proper linguist. Upon the entrance of a cockney speaking, or rather improper, young flower girl. Pickering bet Higgins that he could not train her to be proper to pass as a lady at the ambassador's ball. After dismissing this remark, it is to Higgins' surprise when the girl is found at his front door the following morning. She presents herself as Liza Doolittle and offers to pay him a shilling to teach her to speak proper English for her to be able to work at a flower shop. Recalling Pickering's joke of a bet, Higgins decides to take Liza as his experiment in order to convert her to a proper, well-mannered English lady. With permission from her father to do so, Higgins begins to change everything about Liza that she has ever come to know, starting with her name. She was now to present herself as Eliza Doolittle, daughter of Alfred Doolittle and student of Professor Higgins. During the span of several months, Higgins, with the help of Pickering,

transforms Liza into a proper young woman who is completely unrecognisable. Liza grows to abhor what Higgins had done to her and resent him for attempting, and succeeding at changing her. This tale tells the story of societal expectations and their effect on the minds of all ages, especially the young and the old.

In essence, Liza Doolittle's character can be described with the word 'cockney', explaining the dialect and nature of the East London lower-class, which is reflected throughout Liza's character. Prior to her conversion, she often spoke to adults with what appeared to be coarse language and improper grammar, which was Higgins' first step in correcting her. In this piece, it can be seen that Liza and her future self, Eliza, are to be perceived as different characters. With this being said, Liza plays an important part in the piece as both her present and future self, as she represents a direct standard for what one would believe a poor class citizen would embody, this being rude and dirty, as she is often described by Higgins. Her importance in the piece is not only her drastic character development, but also by demonstrating her contrast towards other characters, especially Professor Higgins, who was wealthier than her. Liza Doolittle's character is representative of the purity of a young mind facing the wrath of societal standards. Her character is significant to the piece since she demonstrates how one can be changed so gradually by societal pressure, and features the purity of a young mind while exposed to manipulation.

Analysis

Origins of Greek Mythology

The title of *Pygmalion* relates to a figure in Greek mythology of the same name, who follows a story which is allegorically similar to that of Shaw's. Pygmalion was a Greek king and sculptor who fell in love with his creation, named Galatea, who then came to life. In the piece by Shaw, it can be inferred that Professor Higgins represents Pygmalion and Liza represents Galatea throughout his narrative; in the play, Higgins often refers to Liza as his experiment, as shown in the line "Yes: in six months - in three if she has a good ear and a quick tongue - I'll take her anywhere and pass her off as anything," (Shaw 32). After he succeeds at this, Higgins believes that Liza had come to life after he carved her, as Pygmalion had done. Higgins, as did

Pygmalion, later falls in love with his creation, being Liza. The reference to Pygmalion from Greek mythology speaks to Higgins' character by demonstrating his attempts to strip Liza of her human qualities, only to fall in love with an ideal mold which he made himself. However, Higgins' egotistical grasp on Liza speaks to her importance by showing that although one can be manipulated to a dangerous point, it is much more difficult to strip one of their values. In the case of Shaw's *Pygmalion*, Higgins represents society and Liza, a young mind, which delivers the manipulated society that Shaw feared. When Liza refuses to marry Higgins, she shows that she is not just an experiment, but a human being who has kept her morals. At the end of the piece, Liza even opens her own flower shop, which shows her true values which she had from the beginning to the end, and how important one's beliefs are to human nature. The relevance of Shaw's relation to Greek mythology demonstrates the truth in Liza's story, and although the piece is comedic, it exhibits the wrath of society on young minds and its ability to torture one into changing their personas from fear and manipulation.

The use of Juxtaposition

In literature, characters which contrast one another, otherwise said as one's foil, can show how a character acts within conflict or even collaboration with one who differs from them, thus highlighting their primary features even further. Though one may consider Higgins to be a foil of Liza, the protagonist, this can be dismissed through comparing their personas. Liza and Higgins are both presented as rude, though Higgins is more entitled while Liza is more stubborn. The sole difference of their qualities lies within their social classes, as Shaw demonstrates. Higgins acts from his power while Liza has none, which can show that although they may appear as foils of one another, it is solely the imbalance of power that stands between them. When Higgins alters Liza's persona into her second nature, Eliza, they differ far more from each other. Since Liza and Eliza, although the same person, are to be seen as different characters, it is truly Eliza who provides a foil to Higgins. As for Liza, it is rather her interactions with Colonel Pickering which are more significant to the effects of foil. Pickering, unlike Liza, is prosperous and well-mannered, which Liza responds to. When Higgins yells at Liza to follow his instructions when reciting the alphabet, Pickering simply tells her, "Good. Splendid, Miss Doolittle," (54), to which Liza responds nicely. In the instance of this piece, Shaw uses Pickering as an unexpected

foil to Liza to allow her innocent, childlike nature to be shown. This adds to Liza's character, as it serves as a reminder that although she speaks brutally throughout the piece, she is a naive mind being manipulated.

Themes of Societal Identity

As stated previously, it can be seen that Liza and Eliza are to be classified as two different characters. This lays the importance of the most prominent theme of the play, this being appearance versus identity. In contrast to Liza, Eliza behaves in every way she does not; she is taught to be proper in a way that reflects the standards of the 20th century, and is pictured as the appearance of a rich woman of the time. However, it is their core identity that can connect them as one character. Though it can be inferred that Liza and Eliza are to be a foil to one another, it is their values that allow them to remain the same through their essence, which Shaw proves is more important than appearance. While analyzing the theme of appearance versus identity, it can be seen that the characters of Liza and Eliza, while the same person with different appearances, remain true to their identities. This can be prominently seen when Eliza opens a flower shop in the Epilogue after following Pickering's suggestion. It is stated by narration, "And so it came about that Eliza's luck held, and the expected opposition to the flower shop melted away, (112)." This narration demonstrates how Liza returned to her nature and opened the flower shop that she had always wanted in lieu of marrying Higgins. In addition to this, Shaw continues to refer to Eliza by the name Liza, even after she had been changed by Higgins. This demonstrates his intention of implying Liza's importance to the play, and how her appearance might have changed by Higgins, the symbol for society, her identity remained the same.

Commentary on the Wealth Gap

Aside from its essence of character interplay and development, *Pygmalion* is a commentary on the English social class system during the 18th century. This piece is comparable to *Animal Farm* by George Orwell, which is allegorically a mockery of the Russian Revolution through characters representing historical figures during the time. Shaw's intentions regarding the themes of *Pygmalion* started by following the original Greek story, though escalated into a

mockery of classes. When examining the characters of Liza and Higgins, it can be inferred that they are to represent the utmost stereotypes of people on opposite sides of the social class spectrum; while Higgins is a prosperous, arrogant man, Liza is a degenerate, impoverished girl. Either way, Shaw means to say, the outcome is disagreeable. In a time with extreme poverty and wealth, Shaw exhibited both sides of the line, and mocked them both by showing one as disagreeable as the other by the two personas. Since Shaw lived in poverty during his childhood, he would have based Liza as a stereotype of poverty based on what he knew and Higgins on his perception of the rich at the time. In addition to this, it can be inferred that Shaw's political perspective during his lifetime had an effect on the way in which he portrayed his characters. For example, the message of his piece could show his socialistic beliefs, especially through the portrayal of Eliza and Higgins. Aside from being a mockery of the English class system at the time, it can be argued that Shaw firmly believed in the diminishing of the wealth gap, and showed this through the contrast of his two protagonists. Throughout the piece *Pygmalion*, George Bernard Shaw executed not only a successful allegorical play, but a powerful theme surrounding appearance and identity which demonstrates the importance of societal expectation on people with differing experiences.

Conclusion

In conclusion, George Bernard Shaw's characterizations in the play *Pygmalion* enriched the themes and symbols in the piece. Through the use of commentary on societal issues, along with the realistic characterizations expressed through temperaments and dialogue, Shaw presents a successful representation of an English society during the 18th century.

References

Cukor, George, director. *My Fair Lady*.

Shaw, George Bernard. *Pygmalion*. Het Spectrum, 1986.

Orwell, George. *Animal Farm*. 1998.

Weintraub, Stanley and Stewart, John I.M.. "George Bernard Shaw". *Encyclopedia Britannica*,
29 Oct. 2020, <https://www.britannica.com/biography/George-Bernard-Shaw>.
Accessed 7 May 2021.

Democracy and the Tibetan Exile Community
A Critique of the Unique Features of the Charter of Tibetans-in-Exile by Ahaan H.
Chhatwal

Introduction

This paper analyzes and discusses the genesis of the nascent democratic form of government in the Tibetan exiled communities and several of the unique characteristics of the Charter of Tibetans-in-Exile, referred to as “the Charter”, that went into effect in June 1991. It aims to identify how effective the Charter has been to transition to democratic governance, and the broader implications of this for the Central Tibetan Administration (CTA), also known as the Tibetan Government-in-Exile (TGiE).

Part I of this paper outlines the historical context of the Tibetan exiled communities and the decision by the 14th Dalai Lama to cede his political authority in order to encourage the adoption of an elected democratic form of government. Part II of the paper analyses of the Preamble and Directive Principles (Chapter 1) of the Charter. In Part III, the paper argues that there are elements of the Charter that are inconsistent with the democratic ideals on which it is based. Lastly, Part IV discusses the extent to which international support for Tibetan exile communities is derived from having a democratic form of government.

This paper makes the following arguments: (1) Tibet's experiment with modern democracy has made significant progress since the inception of its exiled government; however, there remain limitations which hinder the process of becoming a fully realized democracy. (2) Given that no major steps have been taken in the democratic transition of the CTA post the devolution of The Dalai Lama's political powers in 2011, it is more likely that the Tibetan experiment with democracy is inconsequential to the CTA's ability to obtain international support in the past decade; this support could be more greatly motivated by the foreign policy of India and the US concerning China.

PART I: Historical Context and Devolution of Dalai Lama's Political Powers

A Brief History of Tibet

Tibet existed as a de-facto independent state of the People's Republic of China (the "PRC") between 1912 and 1951, with the city of Lhasa as its capital. The term "de-facto" indicates that the state functioned as a subnational territory of China that was not completely recognized as independent yet experienced a high degree of autonomy from the central government in Beijing which exerted little or no control over it. For centuries, the government of Tibet resembled an authoritarian regime, or as Jane Ardley has described, an absolutist theocratic state led by the religious and political leader the Dalai Lama (350).

With the Chinese annexation of Tibet in 1949-50, the PRC gained control of the region. For nearly a decade, the Tibetan government remained in place under the occupation of the Chinese army. However, the Tibetan uprising of March 1959 sparked a military crackdown which caused the 14th Dalai Lama to flee to India with some eighty thousand other Tibetans establishing what became known as the Central Tibetan Administration in Dharamsala ("Brief Introduction to Tibetan Government In-Exile" [officeoftibet.com]).

The CTA, also known as the Tibetan Government-in-Exile, served as a "continuation of the government of independent Tibet" that sought to govern the exiled Tibetan communities ("Brief Introduction"). Meanwhile, the Tibetan homeland continued to be under the control of the PRC and became known as the Tibetan Autonomous Region (TAR). A principal goal of the Tibetan exiled communities has been to regain "genuine autonomy" in the region.

In 1963, shortly after the establishment of the CTA, His Holiness the Dalai Lama promulgated a draft democratic constitution for future Tibet. In 1991, the constitution was replaced by the Charter of Tibetans-in-Exile. The Charter has undergone a series of amendments reflecting a continuous process of democratization, characterized by the separation of powers between three branches of government: the Executive, Legislative and Judiciary. The most notable, however, is the 2011 amendment when the Dalai Lama devolved full political authority to the popularly elected leadership - Sikyong (Political Leader/President).

Function of the Charter of Tibetans-in-Exile

A key reason why the CTA established a Charter is to rehabilitate and restore the freedoms of Tibetan refugees after the Chinese occupation of their homeland. With the aims of further democratization, the Charter was established as “the supreme law of the governing functions of the CTA” (“Charter of the Tibetans in Exile” [tibet.net]). It is the core document that defines the laws and principles of the Tibetan Government-in-Exile, and is the central instrument for governing for the exiled Tibetan communities. Moreover, it is designed as a model for governance when the day comes that there is genuine autonomy in the TAR. However, this will remain an unrealized goal as long as Tibetans in the TAR continue to be under the dominating control of the Chinese government.

Top-down Democratization

The first notable element of Tibetan democracy is that it was not created by a mass political movement, such as when people living under colonial rule or an unpopular monarchy demand rule of the people from the bottom-up. Instead, in this case, it appears that a somewhat reluctant exiled population were given the gift of democracy by the Dalai Lama. This has been aptly captured in a 1990 illustration by Lobsang Gyatso, a cartoonist for the Tibetan Review, comparing the demand by Eastern Europeans for democracy with the birth of democracy in the exiled communities.

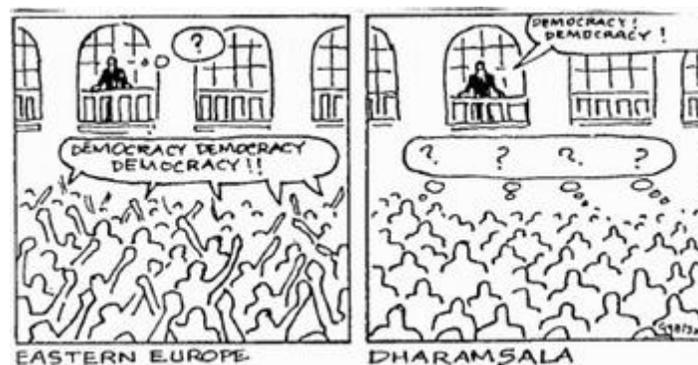


Figure 1: Tibetan Democracy (cited in Frechette 117)

The panel on the left in Figure 1 represents the protests (demanding democracy “from below”) in Eastern European countries such as Poland, Hungary, East Germany, and

Czechoslovakia that replaced communist regimes with democratically elected governments as the Cold War came to an end. The panel on the right, in contrast, shows the Tibetan exiles who are being given democracy “from above.” When a member of the first Tibetan legislature within the exiled communities was asked how the Charter was created, ushering democracy into the Tibetan exiled communities, he answered: “The Dalai Lama said so.” (qtd. in Sangay 122, Interview of Gyakpon Kesang Damdul by Lobsang Sangay, 11 Nov. 2000).

The 2011 amendment to the Charter of Tibetans-in-Exile provided the basis for the transfer of all political authority from the Dalai Lama to a popularly elected government. This was an essential step in the top-down democratic transition of the Tibetan Government-in-Exile. The CTA has also taken smaller steps that reflect its continuous process of change. For instance, the current Charter has been amended from the previous 1963 Constitution to omit mentions of the Lord Buddha as the ultimate source of democracy. This could be seen as quelling concerns about whether the Charter represented a modern democracy or was still clinging to spiritual forms of authority. Perhaps because the Charter was purportedly inspired by the American model (Frechette 108), it was evidently determined that the Charter should reflect modern political principles instead of traditional religious ones.

De-facto Government Model

The term ‘de-facto’ is noteworthy when discussing the current government model and political identity of the Tibetans-in-Exile. It is indicative of a status that is temporary in nature and lacking formal recognition of the CTA and Tibetan exiled communities as anything approaching a sovereign nation. Given its lack of international recognition, the CTA has been described as “something akin to a private NGO [non-governmental organization] under the patronage of the Dalai Lama” (Mills 59).

Unique Features of the Tibetan Exile Community

The territory of the Tibetan exiled community is not based on formal boundaries but instead occupies the imaginations of the people-in-exile based on the collective memory of an ‘old Tibet’ before Chinese occupation and the idea of a ‘free Tibet’ to which they hope to return (Ardley 351). Since the CTA seeks to govern diaspora communities in the territory of foreign

nations across the world, its jurisdiction draws legitimacy from its acceptance by the Tibetan people. The lack of a physical territory does make their attempt at implementing democratic governance unique.

Another interesting feature is the “Green Book” also referred to as the “Rangzen Lakhdeb,” which translates to “Freedom Booklet”. It acts as an identification document of Tibetan citizenship. A Tibetan-in-exile must make Green Book payments to be eligible to vote in the CTA election process (“Pay Green Book” [tibet.net]). The Green Book could be called a “de-facto Passport,” since it is an official CTA identification document although it is not recognized as such by any other country or international organization.

The CTA has established representative offices in 13 countries. These offices are said to act as “de-facto Embassies,” as described by the Department of Information and International Relations (DIIP) of the CTA. Tibetan settlements across the globe can establish Local Tibetan Assemblies and/or Settlement Offices, based on population size, creating an independent local governance framework outside the Dharamsala-based Government-in-Exile.

The CTA also claims a national flag, national anthem, and national language. These are symbols usually associated with the national identity of an independent nation – which Tibet is not. Nor is a return to an independent and sovereign Tibet the policy of the CTA. Instead, the CTA adheres to the policy of the Middle-Way developed by the Dalai Lama. This approach advocates for genuine autonomy in the TAR rather than the status of a fully independent nation of Tibet. Hence, without the status of nationhood, it can be said that these elements are also “de-facto National Identity Elements” of the CTA rather than of an internationally recognized nation.

PART II: The Preamble and Directive Principles

Function of the Preamble

Unlike the preambles of most constitutions, the preamble in the Charter of the Tibetan-in-Exile makes an explicit effort to create an official version of Tibet’s place in history from 2nd Century BC to the present day. It serves three main purposes: to legitimize the right to self-government of the Tibetan homeland by citing the historical roots of the Tibetan people, to

retain support from the host country of the government-in-exile, and to generate international opposition against China's occupation of the Tibetan homeland by highlighting the unjust nature of this occupation, which has taken steps to suppress Tibetan language, culture, and religious practices in the TAR.

The Charter's first paragraph establishes the Tibet of the *Purgayal* period to be one of the three historically great powers of the region, alongside Mongolia and China, advancing the claim that Tibet has always been separate from China. This appears to be aimed at refuting the PRC's rhetorical claim that Tibet has always been a part of China and serves to de-legitimize the PRC control in the contemporary context.

The parallel drawn between the religious and socio-cultural development of Tibet and that of the "holy land of India" attempts to demonstrate Tibetan appreciation of India and emphasize the similarities between the Tibetan and Indian cultures. This is an evident attempt by the CTA to align itself with its host country and reflects the importance of continued support from India to the Tibetan exiled communities. It is difficult to imagine the survival of these communities, over the past 62 years, without the generosity of India.

The preamble contends that "the 17-point agreement had been signed under duress." This refers to a document signed by representatives of Tibet who arrived in Beijing, in the wake of the 1949 PRC invasion of Tibet, seeking to negotiate a secure future of an autonomous Tibet. The PRC invokes this document as evidence that Tibet voluntarily acquiesced in PRC control of the TAR. The inclusion of such claims in the preamble's official history helps fortify the Tibetan narrative of the unjust occupation that followed the 1949 invasion.

Structure and Principles

The CTA consists of three co-equal branches of government based on the separation of powers. The Kashag (Cabinet), which is the executive body, consists of the Sikyong (Political Leader/President) and no more than seven Kalons (Cabinet Ministers). The TPiE is a unicameral legislature composed of forty-five members including a Speaker and Deputy Speaker are elected by the members of the legislature. The third branch, the judiciary, is occupied by a Chief Tibetan Justice Commissioner and other Justice Commissioners.

Article 3 of the Charter conveys the intention for future Tibet to be founded on the principles of – most notably – freedom, democracy, and self-government. This indicates the

CTA's desire to attain genuine autonomy in the Tibetan homeland and to have a separate political system independent from the PRC. Outlining such future desires in this already unique document further reinforces its function as a precursor to genuine autonomy in the TAR and as something that could be instrumental in the achievement of the goal of a self-governing Tibet.

Moreover, Article 4 of the Charter provides that the CTA shall adhere to the principles enshrined in the Universal Declaration of Human Rights of the United Nations. Although the CTA has no membership in the UN, it clearly states a commitment to the principles of the UN, which could possibly attract greater support for the Tibetan cause from the international community. Article 6 of the Charter assures compliance with international law and, in particular, with the laws of the host countries, portraying itself as a respectful and like-minded political entity.

PART III: Aspects of the Charter that are Inconsistent with Democratic Ideals

Retained Political Power of the Dalai Lama outlined in Article 1 of the Charter

Despite the Dalai Lama having ceded his political powers in March 2011, Article 1 of the Charter confers a political role for the Dalai Lama. Although the aim of the 2011 amendment was to devolve the full political authority of the Dalai Lama, this article describes the Dalai Lama as the "Supreme Leader," a term generally associated with heads of authoritative regimes, such as North Korea, where successive members of the Kim family have ruled there as Supreme Leaders since 1948. Formalizing this role for the Dalai Lama, which may be understandable as a sign of the esteem in which he is held by all Tibetans, is not consistent with democratic principles.

Along the same lines, subclause 2 of Article 1 declares it the "responsibility" of the Dalai Lama to "provide suggestions" to the Kashag and TPiE on matters of a political nature. This raises the question of the extent to which the Charter is genuinely an instrument of democratic self-governance if the Dalai Lama continues to occupy a political role – although a diminished and primarily advisory position – after having renounced his political authority in favor of the of democratic institutions set forth in the Charter.

Extended Government Responsibilities outlined in Chapter III of the Charter

One feature of the Charter is that it imposes affirmative obligations on the CTA to promote the welfare of Tibetans in the exiled communities. For instance, Article 17 requires that every child have the right to education and states, somewhat paternalistically:

“Arrangement must be made to provide expert counselling and guidance to the students to enable them to make the right choices regarding their educational future and career.” (The Charter of Tibetans-in-Exile [Approved at the 10th session of 16th Tibetan Parliament-in-Exile], sub-clause 5, art. 17, sec. 3)

This can be seen as the state imposing certain ideas of what is ‘right’ for an individual in line with a government agenda, as opposed to free choice. In contrast, Article 29 of the Indian Constitution concerns the rights of religious minorities but makes no attempt to direct students to make educational or career decisions guided by the state.

Article 17 of the Tibetan Charter further states that

“By fostering and holding in public esteem the master craftsmen and other experts in their respective fields which are in danger of becoming extinct, efforts should be undertaken to preserve and promote the ancient Tibetan culture in general terms and, especially, in the fields of performing arts; the handicrafts and craftsmanship involving the forging, curving or casting of various kinds of materials such as iron, copper, gold and silver.” (The Charter of Tibetans-in-Exile [Approved at the 10th session of 16th Tibetan Parliament-in-Exile], sub-clause 13, art. 17, sec. 3)

This suggests that those engaging in certain professions in the realm of arts and crafts should be held in higher esteem and are deserving of special affirmative action to ensure the protection and promotion of these endeavours. It is unusual for the constitution of a democratic government to explicitly direct its society to favour certain professions.

Robust democracies are not known to exert such control over the personal choices of their citizens, such as education, career, or engagement with culture. To the extent the Charter reflects an obligation of CTA to exert a degree of control over its citizens, this could be regarded as contrary to traditional democratic ideals which guarantee a high degree of individual rights.

Issues with Green Book Payments and Voting

Green Book payments, also known as the payment of Chatrel, are monthly contributions which Tibetans must make to the CTA according to the stipulated rates. This is a responsibility of all Tibetans as stated in subclause 4 of Article 13 of the Charter of Tibetans-in-Exile.

The CTA website indicates that the payment of the contribution is a “condition to gain voting rights in parliamentary elections” (“Pay Green Book” [tibet.net]). However, this contradicts Article 11 of the Charter which states that any citizen who has attained 18 years of age has the right to vote. The Charter itself does not specify that Green Book contributions are necessary in order to vote.

Another issue is that the minimum stipulated rates are mandatory, regardless of employment status, in order to acquire a Green Book. This creates barriers to acquiring a Green Book for those who cannot afford to pay, as indicated in SARD fund’s 2020 Baseline Study of Tibetan Diaspora Community Outside South Asia, in the section concerning Tibetan Associations in Europe, Australia, New Zealand, and East Asia (Samten and Sharngoe 24). This is important since the Green Book is used for school admission, school or university scholarship, and employment within the exile community, and it is said to be essential to claim Tibetan citizenship in the future (“Pay Green Book” [tibet.net]).

The Baseline Study also pointed out disparities in the percentage of the population that make Green Book payments – ranging from 35% of the population in Europe and East Asia to 100% in Australia and New Zealand (Samten and Sharngoe 24). One of the recommendations of the study is the creation of a system for online payments to facilitate collection of Chatrel while being mindful of the need to maintain alternatives for persons who lack access to or familiarity with computer technology (Samten and Sharngoe 33).

Issues with Political Representation

Several elements of the Charter that refer to political representation are noteworthy, including several which are inconsistent with democratic principles.

Although Chapter II, Article 11 of the Charter states that any Tibetan who is 25 years of age has the right to run as a candidate for the Tibetan Parliament, this right is highly circumscribed by the Charter's reservation of seats for regions and ethnic groups, religious schools, women, and representatives of Tibetans overseas as per Chapter V, Article 37.

Reserved Seats for Regions, Religious Schools, and Women

Ten seats (two of which must be held by women) are reserved for each of the three traditional Tibetan provinces of U-Tsang, Dhotoe (Kham), and Dhomey (Amdo), amounting to a total of 30 seats of which at least 6 are reserved for women. Two seats are reserved for each of the five religious schools of Nyingma, Kagyu, Sakya and Gelug and the Yungdrung Bon religion, amounting to an additional 10 seats. Together, the regional and religious representatives make up 40 of the 45 seats in Parliament (*The Charter of Tibetans-in-Exile* [Approved at the 10th session of 16th Tibetan Parliament-in-Exile], art. 37, sec. 5).

In the 1980s, the Dalai Lama proposed non-designated elections to the Parliament, formerly known as the Assembly, upon advice from the Tibetan Youth Congress. This would have led to a reduction or elimination of the reserved seat system. However, this was fiercely resisted by minority groups. Without reserved seats, it was feared that the Parliament would be dominated by central Tibetans and the Gelugpa Buddhists, and other minority groups, such as the Khampas (eastern Tibetans), would be excluded from political power (Frechette 111). It is also possible that no women would be elected without having seats for which only women are eligible.

The former Sikong (President), Lobsang Sangay, has described this reserved seat system as a form of "proportional representation based on the religious sects and regions of Tibet" (Sangay 126). This is not a traditional definition of proportional representation, which is based on allocating seats according to the proportion of votes received by parties or groups running

candidates, and not reserving seats for particular regional, ethnic, and religious representatives (“How proportional representation elections work” [fairvote.org]).

The reserved seat system has also been criticized for resulting in limited political accountability. The opinion of a teacher from the traditional Tibetan province of Kham illustrates this point: “they [Members of Parliament (MPs) representing the Kham region] represent this half-real place of Kham – where I’m from – but what can they ever do in Kham? Sure it is occupied by the Chinese!” (qtd. in McConnell 135). McConnell explains that “half-real” refers to the lack of a fixed spatial constituency as contributing to a communication gap and lack of accountability between MPs and the constituents they purport to represent. The problem also lies in that MPs may fail to grasp local issues and implement policies of interest in far-flung local communities since most MPs reside in Dharamsala (McConnell 135).

Democratic Paradox of having few seats for Tibetans Living Abroad

The only amendments that have been made to the composition of the TPiE outlined in Article 37 of the Charter since its inception in 1991 are as follows:

1. Two seats are now reserved for members from amongst the Tibetans residing in North and South America (previously the two members were from the US and Canada only)
2. Two seats are reserved for members from amongst the Tibetans residing in Europe and Africa (previously the two members were from Europe only)
3. An additional one seat is reserved for Tibetans residing in Asia (excluding India, Nepal, and Bhutan), Australia and New Zealand (making the parliament of a strength of 45 members, which was previously 44)

Although these changes allow for the representation of the diaspora community that has extended to newer geographical locations covering all inhabited continents, they do not allocate seats in proportion to the population of Tibetans living abroad – beyond those residing in the traditional exile communities in India, Nepal, and Bhutan (termed here as South Asia). Traditionally, the number of seats allocated in a democratic legislature is related to population.

Since 1991, the population of Tibetans residing outside of South Asia has increased dramatically to the point that it is approximately equal to the Tibetan communities in South Asia, as confirmed by the SARD fund's 2020 Baseline Study of Tibetan Diaspora Community Outside South Asia. If this trend continues, a majority of the exiled community will live abroad, and the traditional exiled settlements will be in the minority. However, should the seats allocated to communities outside of South Asia not increase, the Tibetan parliament will risk unequal representation, contrary to democratic principles.

Lack of Political Parties

According to Robert Dahl, the need for political leaders to compete for support is an essential element of any robust democracy. The Tibetan Government-in-Exile does well with respect to Dahl's characteristics of democracy (qtd. in Ardley 350), especially after the Dalai Lama dissolved his political powers. However, it is lacking in one key feature in that there is no formal role for political parties within the CTA, leaving voters with no electoral choice between clear policy agendas. Elections are held only for individual candidates and not between two or more competing parties with identifiable policy platforms. Rather, the CTA can be seen as an example of a single-party rule, which is more common in non-democratic regimes (Ardley 352).

There appears to be a belief that competitive political parties are inimical to unity within exile communities, and that unity is of higher value (Dhargyal 41-42). As indicated by a former member of the Assembly of Tibetan People's Deputies (the former Parliament) in a 1997 interview (qtd. in Ardley 357), opposition in Tibetan society was synonymous with the disloyalty of the Dalai Lama, which was considered wrongful from a religious viewpoint.

The only political party in the Tibetan exile community is the National Democratic Party of Tibet which was founded in 1994, but there is no provision for the party to play a role in the exile administration (Ardley 355). The Tibetan Youth Congress, the world's largest Tibetan NGO, is often seen as the de-facto opposition to the CTA, primarily because it takes on a more militant political stance on the independence of Tibet, which diverges from the non-violent policy of the CTA and the Dalai Lama's Middle-Way approach (Roemer 108).

In the early 2000's, the Parliament's agenda included consideration of amending the Charter to accommodate a multi-party system so as to provide for a more robust democratic administration (Ardley 355). As yet, this has not occurred. The fact that such an amendment has

been considered signals some recognition that a multi-party system may be desirable. For instance, some Tibetan citizens in the exiled communities have expressed frustration about not being able to hold accountable those whom they elect (McConnell 134). To the extent that this reform has not occurred, possibly due to opposition from within the Parliament or CTA, suggests that the development of political parties that truly represent the diverse desires of the exiled population, if it occurs at all, will do so when the CTA and the Parliament comes to understand that competitive political parties will not lead to divisiveness that cannot be tolerated.

PART IV: Broader Implications of Tibetan Democracy

Tibetan Democratization as a means to Maintain International Support

It has been observed that, over the long term, exiled communities tend to experience decreased international support.

“Foreign support tends to decline over time. Once an international patron realizes that the political system in the home country is established is unlikely to be overthrown and/or the exile struggle does not have any measurable success, it will limit its support.” (Roemer 49)

Despite consistent efforts to gain genuine autonomy in the Tibetan Homeland, as characterized by the CTA and the Dalai Lama’s proposed ‘Middle-Way’ approach, it appears that little or no progress has occurred in attaining this goal in the 60-plus years since the exiled Tibetan communities were first established. However, contrary to the expected course outlined by Roemer, the CTA has gained increasing support over the years.

Consolidated fund of CTA for the last 10 years

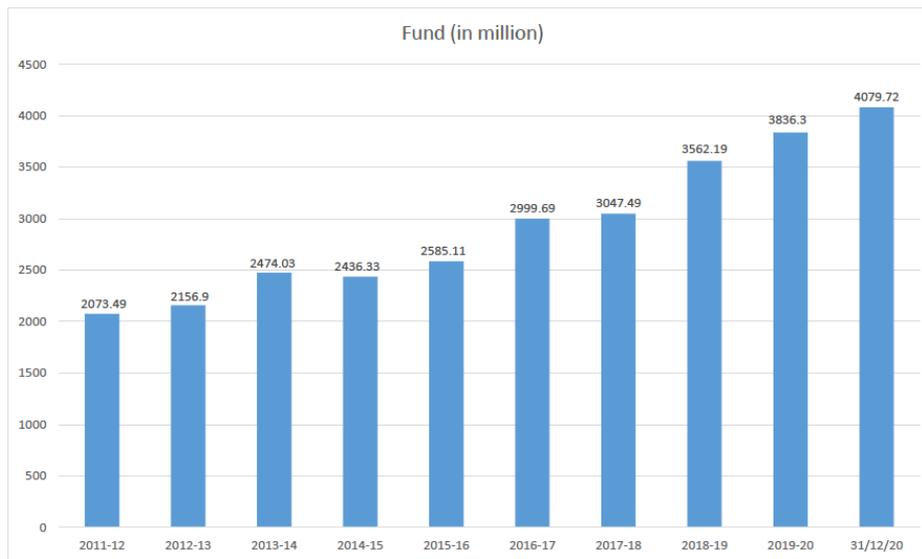


Figure 2: Consolidated fund of CTA for the last 10 years (Source: “Kashag made additional 2,006.23 million rupees in last 10 years” [tibet.net])

The total consolidated fund of the CTA has nearly doubled in the last ten years, increasing from 2,073.49 million rupees in 2011 to 4,079.72 million in December 2020 ("Kashag made" [tibet.net]). The CTA's top-down democratization could provide an explanation for this phenomenon. Governments often pursue top-down democratization when democratic reforms seem necessary for a regime's survival, which in the case of a government-in-exile, depends on retaining support from the host country and the wider international community. This suggests that the decisions of the Dalai Lama and the CTA to pursue a democratic transition, which was furthered by the devolution of the Dalai Lama's political powers in March 2011, may have been motivated by a perceived need to garner increased political and financial support from abroad and in particular from democratic governments.

The process of democratization can thus be seen as linked to the Tibetan struggle for autonomy. Through Roemer's research on Tibetan NGOs, she indicates that "it became evident that the promotion of democracy, human, eco [ecological], and women's rights have been increasingly used to raise awareness in the international community for the exile Tibetan struggle" (123). Moreover, the CTA's increasingly democratic government model is juxtaposed

against the model of centralized power of the Chinese government, enabling Tibetans to deploy against the Chinese government (Ardley 359). However, Ardley also points out that, separate and apart from the objective of gaining international support, ensuring a smooth transition to effective leadership in the event of the Dalai Lama's death could also be an alternative reason for the CTA to pursue a democratic transition.

Support from India and the US and the Concept of Self-interest

Both India and the US have been crucial sources of funds to the CTA, and while the CTA's democratic transition may have played a role in attracting this level of support to some extent, geopolitical circumstances suggest that the support from these two countries may be motivated more out of their own vested interests. In essence, there has been no major democratic transition or reform in the CTA since the devolution of the Dalai Lama's political powers in 2011, but the international support, when measured in terms of the consolidated fund as shown in Figure 2, has almost doubled since.

India provided a relief package to the CTA in 2015-16 for a five-year-period until 2020. According to a September 2020 article of The Economic Times, "The recent border clash with China has revived the proposal to sanction a second tranche of grants to the Tibetan government in exile in India" (Tripathi). This statement indicates how support for the Tibetan exile community is used as a bargaining chip by India in the light of increasing tensions between India and China. Interests like these can be seen to be at the heart of India's long-term pro-CTA policy, as the country has provided support even before the first draft democratic constitution was promulgated by the Dalai Lama in 1963, which arguably marked the beginning of Tibetan democratization. Indian support of the exiled Tibetan government, irrespective of the government of the day, suggests that interests such as national security with respect to China have played a role in influencing support from successive Government of India administrations.

A similar case can be made with respect to the United States. As far back as 1959, when the CIA conducted a decade-long covert program to help the Dalai Lama to flee to India along with thousands of other Tibetans, the US has been a reliable ally to Tibet and the exiled

communities. Upon the declassification of historical documents of in 1998, a Los Angeles Times article reported:

The money for the Tibetans and the Dalai Lama was part of the CIA's worldwide effort during the height of the Cold War to undermine Communist governments, particularly in the Soviet Union and China. In fact, the U.S. government committee that approved the Tibetan operations also authorized the disastrous Bay of Pigs invasion of Cuba. (Mann)

The Dalai Lama also wrote in his autobiography *Freedom in Exile* that the CIA provided assistance in order to “destabilize all Communist governments” (122) and formed part of the USA’s “anti-Communist policies” (192).

More recently, the US Congress, during the Trump administration, enacted two pieces of legislation in support of the CTA. The first was The Reciprocal Access to Tibet Act of 2018 which advocated free travel to Tibetan areas in China. The second was The Tibetan Policy and Support Act of 2019 which formed the basis for the provision of funds to the CTA. A total of around \$26,654,000 was allocated for Tibetan communities for education, overall development, and information and broadcasting for the Tibetan cause. The following summarizes its financial provisions:

“\$1 million for the Office of the US Special Coordinator for Tibetan Issues for each of the fiscal years 2021 through 2025, \$675,000 towards scholarship provisions, \$575,000 for scholar exchange initiatives, \$8 million for TAR and Tibetan Communities in China, \$6 million for Tibetans living in India and Nepal, over \$3.3 million and \$4 million respectively for Voice of America's and Radio Free Asia's reporting on Tibet and \$3 million for Tibetan governance. (“The Tibetan Policy and Support Act,” sec. 7)

This Act also imposed a set of conditions on the PRC in support of protecting the Tibetan identity, including the threat of economic and visa sanctions on any Chinese official who interferes with the succession of the Dalai Lama. Given the general anti-China policy of the

Trump Administration, it is reasonable to attribute this increased support for Tibet not to its continued democratization but to the issues between the US and China. As a January 2021 India Today article stated: “Tibet is a key fulcrum of today's Cold War politics between the USA and China” (Kannan). Consequently, it is possible to view such support as being derived more from the self-interest of the US and India more than from a positive response to Tibetan democratization.

Conclusion

For most of Tibet’s history, it has been a complete theocracy, with the Dalai Lama and his close advisers holding ultimate political and spiritual authority. Democracy and democratic institutions were introduced to Tibetans with the establishment of the CTA as the Dalai Lama fled to India.

As this paper has pointed out, the Charter provides unique structures which enable the self-governance of the Tibetan exile communities. However, some of these structures are not aligned with democratic principles, such as the retained political role of the Dalai Lama, the high degree of government influence in the areas of education, career, and culture, unequal access to the Green Book, and the model for political representation. While the prospects for the future developments of democracy in Tibet cannot be predicted, this paper identifies issues that should be addressed as the Tibetans-in-exile continue their new democratic experiment.

Finally, the paper provides context on the increased international support for the CTA, relegating the foreign policy of India and the US concerning China as a key motivation.

References

- Ardley, Jane. "Learning the Art of Democracy? Continuity and Change in the Tibetan Government-in-Exile." *Contemporary South Asia*, vol. 12, no. 3, 2003, pp. 349–363., doi:10.1080/0958493032000175888. Accessed 25 Jul. 2021.
- "Brief Introduction to Tibetan Government In-Exile." *The Office of Tibet*, www.officeoftibet.com/index.php/2014-08-21-17-03-06/brief-introduction-to-tibetan-government-in-exile. Accessed 8 Jun. 2021.
- Bstan-'dzin-rgya-mtsho, Dalai Lama XIV. *Freedom in Exile: The Autobiography of the Dalai Lama*. New York, NY: HarperCollins, 1990. Accessed 20 Aug. 2021.
- Central Tibetan Administration, Social And Resource Development Fund, Samten, Lobsang Choedon, and Tenzin Dolkar Sharngoe. *Baseline Study of Tibetan Diaspora Community Outside South Asia, 2020*. Accessed 8 Jun. 2021.
- "Charter of the Tibetans in Exile." *Central Tibetan Administration*, tibet.net/about-cta/constitution/. Accessed 1 Jun. 2021.
- Constitution of Tibet. Promulgated by His Holiness the Dalai Lama, 10 Mar. 1963, <http://www.tibetjustice.org/materials/tibet/tibet2.html>. Accessed 5 Jun. 2021.
- Dahl, R. "Polyarchy: Participation and Opposition" (New Haven: Yale University Press, 1971), p 3. Quoted in Ardley 350.
- "Department of Information & International Relations." *Central Tibetan Administration*, tibet.net/department/information/. Accessed 8 Jun. 2021.
- Frechette, Ann. "Democracy and Democratization Among Tibetans in Exile." *The Journal of Asian Studies*, vol. 66, no. 1, 2007, pp. 97–127., doi:10.1017/s0021911807000022. Accessed 23 Jul. 2021.
- "How Proportional Representation Elections Work." *FairVote*, www.fairvote.org/how_proportional_representation_elections_work. Accessed 23 Aug. 2021.
- "H.r.4331 - 116th Congress (2019-2020): Tibetan Policy and Support Act of 2019." *Congress.gov*, 30 Jan. 2020, www.congress.gov/bill/116th-congress/house-bill/4331/text?format=txt&r=3&s=1. Accessed 16 Aug. 2021.

Kannan, Saikiran. "All you need to know about Tibetan parliament-in-exile election and its implications." *India Today*, India Today, 2 Jan. 2021, www.indiatoday.in/news-analysis/story/all-you-need-to-know-about-tibetan-parliament-in-exile-election-and-its-implications-1755329-2021-01-02. Accessed 17 Jun. 2021.

"Kashag Made Additional 2,006.23 Million Rupees in Last 10 Years." *Central Tibetan Administration*, 19 Mar. 2021, tibet.net/kashag-made-additional-2006-23-million-rupees-in-last-10-years/. Accessed 23 Jul. 2021.

Mann, Jim. "CIA Gave Aid to Tibetan Exiles in '60s, Files Show." *Los Angeles Times*, Los Angeles Times, 15 Sept. 1998, www.latimes.com/archives/la-xpm-1998-sep-15-mn-22993-story.html. Accessed 16 Aug. 2021.

McConnell, Fiona. "Democracy-in-Exile: The 'Uniqueness' and Limitations of Exile Tibetan Democracy." *Sociological Bulletin*, vol. 58, no. 1, 2009, pp. 115–144., doi:10.1177/0038022920090107. Accessed 23 Jul. 2021.

Mills, Martin A. "This Turbulent Priest: Contesting Religious Rights and the State in the Tibetan Shugden Controversy." *Human Rights in Global Perspective: Anthropological Studies of Rights, Claims and Entitlements*, Routledge, 2003, pp. 54–61. Quoted in Ardley 351.

Norbu, Jamyang. "Opening of the Political Eye: Tibet's Long Search for Democracy." *Tibetan Review*. 11th ed., vol. 25, Tibetan Review, 1990, pp. 13-17. Accessed 21 Aug. 2021.

"Pay Green Book." *Central Tibetan Administration*, tibet.net/support-tibet/pay-green-book/. Accessed 5 Jul. 2021.

"Report to Congress on Access to Tibetan Areas of the People's Republic of China (PRC), Sec. 4 of the Reciprocal Access to Tibet Act of 2018, Pl 115-330 // 22USC 1182." *U.S. Department of State*, U.S. Department of State, 1 Dec. 2020, www.state.gov/report-to-congress-on-access-to-tibetan-areas-of-the-peoples-republic-of-china-prc-sec-4-of-the-reciprocal-access-to-tibet-act-of-2018-pl-115-330-22usc-1182/. Accessed 11 Aug. 2021.

- Roemer, Stephanie. “The Tibetan Government-in-Exile: Politics at Large.” *Routledge*, 2008. Accessed 29 Jun. 2021.
- Sangay, Lobsang. “Tibet: Exiles' Journey.” *Journal of Democracy*, vol. 14, no. 3, 2003, pp. 119–130., doi:10.1353/jod.2003.0063. Based on a paper presented at a conference at Harvard University on “The Cold War and Its Legacy in Tibet: Great Power Politics and Regional Security.” Accessed 23 Aug. 2021.
- Shain, Yossi. “The Frontier of Loyalty: Political Exiles in the Age of the Nation-State.” *University of Michigan Press*, 2005. Quoted in Roemer 46.
- Thargyal, R. “Forming the Nation: the process of polyarchic laterality among the Tibetan diaspora”, in P. Kvaerne and R. Thargyal (eds), *Bon, Buddhism and Democracy: the building of a Tibetan national identity*, (Copenhagen: Nordic Institute of Asian Studies, 1993, report no. 13), pp 41–42. Quoted in Ardley 352 and Frechette 111.
- The Charter of Tibetans-in-Exile*. Assembly of Tibetan People's Deputies, Central Tibetan Administration, 14 Jun. 1991, <https://tibet.net/wp-content/uploads/2011/06/Charter1.pdf>. Accessed 25 Jul. 2021.
- The Charter of Tibetans-in-Exile*. Tibetan Parliament in Exile, Central Tibetan Administration, 2021. Approved at the 10th session of 16th Tibetan Parliament-in-Exile which lasted from Mar. 15-31, 2021. Accessed 4 Jun. 2021.
- Tripathi, Rahul. “Relief Package: Tranche 2 Funds Likely for over 1 Lakh Tibetans in India.” *The Economic Times*, Sept. 2020, economictimes.indiatimes.com/news/politics-and-nation/relief-package-tranche-2-funds-likely-for-over-1-lakh-tibetans-in-india/articleshow/78287999.cms?from=mdr. Accessed 3 Jun. 2021.
- Yangchen, Jigme. “Baseline Study of Tibetan Diaspora Community Outside South Asia': SARD's Pioneering Report Maps Status of Diaspora.” *SARD Fund*, 25 Sept. 2020, sardfund.org/baseline-study-of-tibetan-diaspora-community-outside-south-asia-sards-pioneering-report-maps-status-of-diaspora/. Accessed 8 Jun. 2021

The Role of Plant Hormones (Salicylic acid and Jasmonic acid) in Shaping the Plant Root Microbiome by Juezi Huang

Abstract

Plant microbiomes have important functions in promoting the growth and development of plants as well as extending plant immunity. Notably, plant hormones also show significant impacts on regulating the root microbiome. In this review, we focused on the techniques that are commonly used in the investigation of plant-microbe interactions. The way of the plant hormones salicylic acid and jasmonic acid shaping the microbiome is also discussed. With the improvement in the techniques and the deeper understanding of the communication between plants and microbiomes through plant hormones, a greater crop yield can be achieved.

Key terms: root microbiome, plant-microbe interaction, salicylic acid, jasmonic acid

Introduction

The term microbiome describes the cells and the collective genome of microbial communities that live in a particular habitat¹. The microbiome includes diverse micro-organisms including bacteria, fungi, archaea, and viruses. These communities can be commensal (a relationship between two organisms where one benefits without influencing the other), mutualistic (a relationship where two organisms benefit from each other), or pathogenic (a relationship between two organisms where one causes the disease to the host)². Land plants are continuously exposed to all kinds of micro-organisms including bacteria, fungi, and archaea. Microbiomes can also be found on plants tissues such as leaves, stems, and roots. Moreover, the root-related microbial communities could be further distinguished into different compartments. For example, the endophytic compartment (EC), rhizoplane, and rhizosphere are the distinct compartments of root and the soil surrounding¹.

As the microbiome in the rhizosphere is persistently studied, some important functions of the constituent microbes are revealed, including the acquisition of nutrients, disease resistance, and stress tolerance. For nutrients acquisition, the symbiotic relationship between arbuscular

mycorrhizal fungi (AMF) and *rhizobium* bacteria is widely studied. Some commensal plant growth-promoting bacteria can also provide plants with insoluble minerals and improve the architecture of the root system. Moreover, in the plant defense system, the plant exudates impact micro-organisms in soil as the first defense line against soil-borne pathogens. The microbes associated with plants will alter plant evolutionary responses to environmental stress through at least three pathways that are not exclusive to each other. The pathways include changing the fitness of individual plant genotypes, expression of plant traits related to fitness, and direction of natural selection occurring within populations that experience environmental stress through the microorganisms' effects on reproductive fitness³.

The root microbiome can be varied by different factors. For example, in the research comparing the microbiome in plants in different geographical locations, soil type is found to have a major effect on determining the composition of rhizobiomes⁴. More importantly, the root microbiome is influenced by the plant genotype. The plant exudate is one of the ways plants tune the

microbiome. The root exudates are a mix of all kinds of compounds including carbohydrates, amino acids, and organic acids. These compounds generate the gradient of carbon sources, phytochemicals, oxygen as well as pH and hence influence the root microbiome composition⁵.

Besides plant exudates, plant hormones are also involved in regulating the root microbiome. Plant hormones are the chemicals in plants that are involved in cellular processes. There is a large variety of plant hormones. Table 1 summarizes the major hormones in plants and their main functions. Studies suggested that plant hormones can shape the microbiome by triggering immune pathways⁶. This review will focus on some techniques that are applied commonly to study plant-microbiome interaction and the role of jasmonic acid and salicylic acid in shaping the root microbiome on plants.

Hormone name	Primary functions
--------------	-------------------

Auxin	Auxin is important to the growth and development of plants. The ability of auxin to drive the elongation of hypocotyls, epicotyls, and coleoptiles is widely studied ⁷ .
Salicylic acid (SA)	SA has an irreplaceable role in plant immunity. This hormone is found to take part in both pathogen-associated patterns (PAMPs) triggered immunity (PTI) and induce effector-triggered immunity (ETI). In the meantime, it also has interactions with other plant hormones such as auxin, and ABA to help regulate plant growth and adaption to abiotic stress ⁸ .
Jasmonic acid (JA)	JA is an essential hormone in plants. It is involved in multiple important biological processes in plants. For instance, it involves the plant immunity system, it also has interactions with SA which is mainly related to plant resistance. It also involves the mediation of stress and control stomatal opening and closure ⁹ .
Ethylene	Ethylene is mainly involved in regulating the developmental process of plants. It also involves the stress response of plants. Furthermore, it also shows a response to other plant hormones ¹⁰ .
Abscisic acid (ABA)	ABA is very crucial in regulating the growth and development of the plant as well as seed development. It also involves stress response and controlling the stomata opening and closure ¹¹ .

Gibberellic acid (GA)	GA involves in various biological processes. It takes part in seed dormancy and development, cell elongation, flowering initiation, sex expression as well as embryo development ¹² .
Cytokinin	Cytokinin is found mainly related to the growth and development of plants in all kinds of aspects such as leaf development, root development as well as vascular development ¹³ .

Table 1. Some common hormones in plants and their main functions in plants.

Techniques of investigating plant-microbiome interaction

Arabidopsis thaliana as a model plant

Arabidopsis thaliana is a plant that is widely used as a model plant in studies about botany. This is because it has a small size and a short life cycle last (8-12 weeks). *A. thaliana* is also self-pollinating, and offspring tend to have highly homozygous gene loci. However, it can also be cross-pollinated manually. *Arabidopsis thaliana* also has a very small DNA content with only

100 Mbp per haploid genome. Therefore, its genome is easy to be edited and multiple mutants can be created¹⁴. Several mutants of *Arabidopsis* are already identified to detect the impact of change in host hormone production on the composition of the root microbiome. For example, *sid2* mutation reduces the accumulation of SA; *npr1* causes a deficiency in SA signaling, and *fad7/8/9* is a triple mutant deficient in JA accumulation¹. More importantly, pathosystems can be developed in *Arabidopsis* through two ways: 1. inoculate pathogens from closely related plant species and see whether the pathogens can also cause disease in *Arabidopsis*, 2. Seek for naturally infected *Arabidopsis*. With the development of these

pathosystems that show useful variation in the host response to pathogens, more problems about plant disease could be addressed¹⁴.

Technology to determine the composition of the microbiome

There are multiple techniques used to determine the members of the root microbiome and they can be categorized into culture-dependent and culture-independent methods.

The culture-dependent method were early developed techniques. It aims to study the behavior of the microbes under defined conditions¹⁵. In the study of microbiome, scientists culture micro-organisms in the laboratory for the purpose of characterizing the microbial community¹. For example, one study used transposon sequencing of *Pseudomonas* to identify genes that are related to root colonization of *Arabidopsis*. The culture-dependent techniques might not be expensive but could be time-consuming. One significant limitation of this method is that the microbiome formed in this method is incomplete and has reduced diversity compared to the actual environment¹⁵. Therefore, the microbiome might not be representative¹⁵.

Unlike the culture-dependent method, culture-independent techniques are the molecular biology techniques that bypass the necessity of culturing microbes in the lab. Its biggest advantage is it could show the full picture of the root-associated microbiome. However, current culture-independent techniques still have limitations, as discussed below.

16s amplicon sequencing and shotgun sequencing are the two most commonly used techniques of finding out “Who is there?” in the microbiome. They are both culture-dependent techniques.

In 16s rRNA gene sequencing, the region coding for 16s rRNA is amplified with PCR using primers that recognize highly conserved regions of the genes and sequenced. The amplified sequences are then clustered into operational taxonomic units (OTUs) based on their similarities. Certain assumptions can arise from the clustering, for example, sequences of 95% identity can represent one genus, while sequences of 97% identity can represent the same species. This method shows several advantages¹⁶. First, it requires a relatively low cost. Second, the data analysis can be performed by established pipelines. Finally, there is also a large database for reference. However, the limitation of this technique is that the annotation is based on an assumed

association of the 16s rRNA gene with taxa defined as an OTU. Also, the OTUs are generally analyzed at the phyla or genera level and are less accurate at the species level. Moreover, because only the 16s rRNA gene is sequenced, other genes are based on the predicted OTUs. Therefore, the lack of direct gene identification might limit the understanding of the microbiome because of the existence of numerous bacterial strains¹⁷. Also, in 16s rRNA gene sequencing, the primers targeting the 16s rRNA gene are highly conserved. Therefore, the primers might not only target bacteria but also organelles such as mitochondria. This might influence the analysis of the microbiome that also contains plant materials¹.

For shotgun sequencing, it sequences the whole genome including the overlapping region with random primers. This method owns the strength of having reinforced ability in identifying bacteria at a species level. Due to the increase in length of reads and the assembly of contigs, the accuracy of species detection is also increased. Furthermore, shotgun sequencing has the capacity of identifying specific genes in the microbiota. It has better detection of the diversity and the prediction of genes. However, there are still disadvantages in applying shotgun sequencing: 1) It is more expensive compared to 16s rRNA sequencing, 2) it requires a much more extensive database when analyzing the data¹⁷.

Role of plant hormones: salicylic acid and jasmonic acid in plant-microbiome interaction

Role of salicylic acid in shaping plant microbiome

Salicylic acid (SA) is a plant hormone that is universally appeared in all plants. The basal level of SA varies among different plant species¹⁸. For most of the plants, the SA level is relatively low during the normal growth and development process because a high level of SA may inhibit plant growth and development¹⁹. For example, in *Arabidopsis* the basal level of SA is around 1. a μ M while in other species such as potato and rice the basal level of SA will be higher²⁰. The changes in the surrounding environment will alter the concentration of SA in plants. These changes can be both biotic and abiotic.

When plants are under biotic stress, the SA level increases. For example, when *Arabidopsis* is infected by the fungal biotroph *Erysiphe orontii* or the bacterial necrotroph

Pseudomonas syringae pv. *Maculicola*, the SA level in plants increases²¹. During this process, SA is synthesized from chorismate depend on the ICS (isochorismate synthase) genes. Some bacteria such as *Pseudomonas aeruginosa* is also found to produce SA with ICS. Studies also show that the inoculation of *Mentha x piperita* plants with different rhizobacteria strains may lead to the increase of endogenous SA production¹⁸. The SA level will also increase when plants are under abiotic stress. Heavy metal stress can be one of the most common stresses to plants and could impose serious effects on plants and even humans through the food chain. Research on maize showed that when a plant is exposed to Cd, the SA accumulation will increase significantly. Furthermore, other abiotic stresses such as cold will also induce the production of SA in plants¹⁸.

The mechanism of SA influencing the root microbiome is complex. The SA can influence the root microbiome both directly and indirectly. Multiple lines of evidence suggest that SA could influence the assembly of the microbiome indirectly through an immune response. It could participate in multiple immune pathways especially systemic acquired immunity. The SAR immune response is triggered by local pathogen attack of leaves and leads to plant-wide protection including distal and uninoculated organs²²⁻²³. The study had shown that the activation of SAR can change the rhizobiome in *Arabidopsis*²⁴. Moreover, in another research that used both SA *Arabidopsis* mutants and exogenous application of SA, the root microbiome compositions are both found to be different after applying the two methods. For instance, in the mutant *cpr5* (hyperimmune), nine members of Actinobacteria showed reduced relative abundance while 12 Proteobacteria members showed increased relative abundance. In the experiment that used exogenous SA application, *Terracoccus* sp. 273 (Actinobacteria) was enriched in the root endophytic sample. These results showed SA influences the root microbiome by selecting different bacterial taxa (the bacteria can use SA as a carbon source or a growth-promoting factor) through its function in homeostatic control of immune system outputs²⁵.

These two studies suggest a general mechanism of SA can influencing the root microbiome through participating in immune activation, but a more detailed understanding of the SA-related immune signaling pathways influencing the root microbiome is still needed. The SA can also influence the root microbiome directly. For example, the growth of fungi *Fusarium oxysporum* f. sp. *Niveumcan* is inhibited by SA when it is released as a root exudate in

watermelon²⁶. Furthermore, the hormone SA is also found to be synthesized in some microbes such as beneficial root fungi *Indica* and *Mortierella hyaline*. However, the function of SA produced on plant colonization is still unknown. Studies showed that bacterial-producing SA might also support the growth of bacteria under iron limiting condition²³.

Role of Jasmonic acid in shaping the root microbiome

The hormone jasmonic acid (JA) and its derivatives can be found in higher plant species ubiquitously. They are all fatty acids that are derived from cyclopentanones and belong to the family known as oxylipids. Normally, there are high levels of JA in reproductive tissues, flowers, and seeds. It has been suggested that high levels of JA derivatives in *Zea mays* may be related to sex determination of the male reproductive structure²⁷. However, the level of JA is very low in root and mature leaves²⁸. As observed with SA, the concentration of JA in plants is also influenced by the surrounding environment that includes both biotic and abiotic environmental factors.

When the plant is under attack by herbivory insects, pathogens (specially necrotrophs) as well as wounding, JA can be synthesized rapidly²⁹. All kinds of abiotic environmental factors could also impose changes in the concentration of JA, especially abiotic stresses. For example, when drought happens, there will be a rapid increase in endogenous content of JA and gradually decrease to basal level when drought continues. Moreover, the endogenous JA content was also found to increase to a larger extent when the plant (*Arabidopsis*, tomato, potato) is treated with salt. It is worth noting that the JA concentration increases in salt-sensitive plants but nearly has no change in salt-tolerant plants⁹. To summarize the synthesis process, JA is produced through the consistent action of enzymes in plastids, peroxisome, and cytoplasm. The stresses activate phospholipase in the plastid membrane and promote the synthesis of linolenic acid. The linolenic acid will then be converted to 12-oxo-phytodienoic acid (12-oxo-PDA) through oxygenation with lipoxygenase (LOX), allene oxide synthase (AOS), and allene oxide cyclase (AOC). JA is then synthesized from 12-oxo-PDA by the activity of 12-oxo-phytodienoic acid reductase (OPR) and 3 cycles of beta-oxidation⁹.

Similar to SA, JA can also influence the root microbiome directly or indirectly. The mechanism of JA influencing the root microbiome indirectly is also related to plant immune response, but JA participates in different pathways compared to the SA. In the research that applies exogenous JA to activate plant immune response, the rhizosphere bacterial community is influenced. The bacterial population that was enriched was found to have a close relationship with organisms that involve in plant defense. For example, a *Bacillus* population is found to be enriched upon the activation of JA-mediated immune response. This population is close relative to the strain MHS022 that is known to produce antifungal volatiles acetamide and benzothiazole. However, the bacterial populations that were found to be related to plant growth such as *Bacillus niacini* were suppressed³⁰. The study had suggested that with different modifications of the JA-mediated immune pathways using *Arabidopsis* mutants, both the composition of root exudates and rhizosphere bacteria and archaeal communities are affected, and the changes are found to be correlated to each other. For example, in the mutants of *Arabidopsis myc2* and *med25* (the former one has an increase in expression of defense gene but with weakened wound and insect response while the latter one has weakened herbivory and wound responsive pathway), the release of asparagine, ornithine, and tryptophan was reduced³¹. According to studies, glutamic acid and tryptophan are chemotactic to plant-associated bacteria, including *Rhizobium leguminosarum*, *Bacillus subtilis*, *Bacillus megaterium*, *Pseudomonas putida*, *Pseudomonas fluorescens*, and *Azospirillum brasilense*. These findings proposed the mechanism of JA influencing the root microbiome through changing root exudate composition by regulating immune response³¹. In the root microbiome, some microbes are detected to synthesize JA. For instance, ectomycorrhizal fungus *Pisolithus tinctorius* can synthesize and metabolize JA²³. However, whether the hormone produced by the fungi can influence the root microbiome directly is still needed to be explored further³².

The interactions between SA and JA

A large number of studies suggested that there are complex interactions between the hormone SA and JA. Both SA and JA mediated signaling pathways can be triggered. For instance, when plants are under attack from virulent *Pseudomonas syringae* both SA and JA

signaling pathways will be activated³³. Under certain situations, one hormone signaling pathway will be more prioritized than the other one. For instance, the SA pathway that is induced by avirulent *P. syringae* will suppress the JA-signaling pathway. However, when the *Arabidopsis* is treated by *Pseudomonas sp. CH267*, the systemic susceptibility will be induced³³. The SA and JA tradeoff will shift toward JA dependent pathway against herbivores while sacrificing SA-related defense against bacterial pathogens. When the surrounding environment changes, plants shift between the SA and JA mediated pathways. The change in the signaling might influence homeostatic control and secondary metabolites secreted by plant roots and hence influence the root microbiome composition³².

Techniques that are used to investigate the microbiome

In this review, *Arabidopsis thaliana* is discussed as a model plant. It owns unique characteristics (e.g., short life cycle, easily edited genes, etc.) that make it suitable to be used as a model plant in a wide range of research that is related to plants. The techniques (16s rRNA gene sequencing and shotgun sequencing) of identifying the compositions of the microbiome are also introduced. Moreover, the culture-dependent and culture-independent approaches of analyzing the microbiome are also discussed. These techniques are broadly used for investigating the plant-microbiome interaction. In the studies mentioned in this review, scientists used *Arabidopsis* mutants with altered hormone production and signaling to investigate plant microbiome interactions^{25 31}. Moreover, both studies used 16s rRNA gene sequencing to analyze the microbiome composition.

As mentioned in the review there are limitations on the techniques. Therefore, it is important to have multiple experiments to investigate the impact of plant hormones on the composition of root microbiome more accurately. In the paper written by Lebeis et al., both exogenous applications of plant hormones and *Arabidopsis* mutants are used in the research to find out the mechanism of SA influencing the root microbiome²⁵.

The role of Salicylic acid and Jasmonic acid in shaping root microbiome

Plants and microbes are interacting with each other incessantly. For plants, they are trying to build up attractive habitats for beneficial microbes to colonize. However, this will also introduce pathogenic microbes. Therefore, plants need to build up mechanisms to select and manage the members in their microbiomes³⁴. In this process, plant hormones play an irreplaceable role. To study the complex interactions between plant hormones and the microbiome, multiple techniques are developed. Researchers can investigate the mechanisms of plant hormones influencing microbiomes using combinations of techniques.

This review mainly focused on the plant hormones JA and SA. In the review, the basal levels of the two hormones were discussed and both biotic and abiotic factors can trigger the change in the level of the two hormones. Both of them can influence the plant microbiome directly or indirectly: (1) The two hormones can regulate the rhizobiome through their immune signaling pathways when the plant immune response is triggered. (2) Plant hormone can also make direct chemical interactions with microbes when it is secreted as root exudate or when members of the microbiome produced them. Moreover, under different conditions, the plants will shift their immune signaling pathways toward one than the other one^{26 32}. However, further understanding of the mechanisms of plant hormones influencing the root microbiome is still needed. The function of phytohormone-producing microbes shaping the root microbiome is still needed to be explored further.

Besides focusing on the role of SA and JA shaping the root microbiome, the functions of other plant hormones in shaping microbiomes on other locations of plants are also studied such as the phyllosphere (the habitat for microbes provided by the parts of plants that is above ground) is also being studied³⁵. The communication between plants hormones and microbes is studied in other agricultural plants as well. For instance, plant-microbiome interactions in peanut (*Arachis hypogaea L.*), legume, wheat (*Triticum aestivum*) and, rice (*Oryza sativa*)^{36 37}. With a deeper understanding of the interactions between plant hormones and microbes and the mechanism of hormones regulating the microbiome, an enhanced crop yield can be achieved. For example, understanding of the JA-signaling pathway can be used to attract and maintain beneficial

microbes and breeding microbe-optimized plants as well as specific plant-optimized microbiomes which are useful inoculants³⁸.

References

- Reinhold-Hurek B, Bunger W, Burbano CS, Sabale M, Hurek T. Roots Shaping Their Microbiome: Global Hotspots for Microbial Activity. *Annu Rev Phytopathol.* 2015;53:403- 424. doi:10.1146/annurev-phyto-082712-102342
- Schlaeppli K, Bulgarelli D. The plant microbiome at work. *Mol Plant-Microbe Interact.* 2015;28(3):212-217. doi:10.1094/MPMI-10-14-0334-FI
- Trivedi P, Leach JE, Tringe SG, Sa T, Singh BK. Plant–microbiome interactions: from community assembly to plant health. *Nat Rev Microbiol.* 2020;18(11):607-621. doi:10.1038/s41579-020- 0412-1
- Lundberg DS, Lebeis SL, Paredes SH, et al. Defining the core *Arabidopsis thaliana* root microbiome. *Nature.* 2012;488(7409):86-90. doi:10.1038/nature11237
- Vives-Peris V, de Ollas C, Gomez-Cadenas A, Perez-Clemente RM. Root exudates: from plant to rhizosphere and beyond. *Plant Cell Rep.* 2020;39(1):3-17. doi:10.1007/s00299-019-02447-5
- Kniskern JM, Traw MB, Bergelson J. Salicylic acid and jasmonic acid signaling defense pathways reduce natural bacterial diversity on *Arabidopsis thaliana*. *Mol Plant-Microbe Interact.* 2007;20(12):1512-1522. doi:10.1094/MPMI-20-12-1512
- Korasick DA, Enders TA, Strader LC. Auxin biosynthesis and storage forms. *J Exp Bot.* 2013;64(9):2541-2555. doi:10.1093/jxb/ert080
- An C, Mou Z. Salicylic Acid and its Function in Plant Immunity. *J Integr Plant Biol.* 2011;53(6):412-428. doi:10.1111/j.1744-7909.2011.01043.x Ruan J, Zhou Y, Zhou M, et al.
- Jasmonic acid signaling pathway in plants. *Int J Mol Sci.* 2019;20(10). doi:10.3390/ijms20102479

Binder BM. Ethylene signaling in plants. *J Biol Chem.* 2020;295(22):7710-7725.
doi:10.1074/jbc.REV120.010854

References...etc

From England to Vietnam: Tragic Love Stories Across Cultures by Ha Duong

Introduction

In modern society, when people's material needs are met, the need to search for spiritual culture is inevitable (Little, 2014). In order to meet this spiritual need, people tend to rely upon their customs, traditions, primitive beliefs, or even origins (ibid). Folk beliefs have always been a land containing many mysteries, evoking curiosity in discovering those ancient features as they bring people back to their ancestors and the spiritual values of their nation. Studying the cultural elements in stories is also a way to bring us back to our cultural roots.

Culture, besides reflecting the beauty of lifestyle and generally even a deep belief in some mystical world, helps people to have a more complete awareness of morality, and a deeper view of their ancestors and cultural narratives. This paper will focus on comparing the Vietnamese legend of *My Chau Trong Thuy* (Nguyen, 1905) and the English quintessential love tragedy *Romeo and Juliet* (Shakespeare, 1947). The comparison attempts to explain the differences between the texts exist to reveal how cultural elements contribute to the stories. Moreover, and perhaps unexpectedly, the research reveals that concepts of 'pure love' that are typically only associated with Victorian-era ideals and altogether excluded from the 'Asian tradition' until the 20th centuries are present even in the renaissance eras in Europe and the Warring States periods in East and Southeast Asia (Stearns, 1993).

Even though the stories come from different places and have different backgrounds and geographies, they share important details in common, which may appear in the situations or the endings. However, there are differences within the parallels. I explore the likeness and the disparities, the variety in cultures, traditions, perspectives as well as how those elements influence the stories will be explored. Stories can serve as a tool to preserve cultures and to help the next generations learn from their ancestors (Christine, 2012). Seeking to uncover the reasons behind the similarities and differences promotes intercultural awareness and helps us better understand our shared narratives and themes across humanity and at different ages.

In order to achieve the goal of the research, the analysis encompasses elements inside and outside the stories. This paper will also include historical contexts, and a brief summary of the

two stories: *Romeo and Juliet* and *My Chau Trong Thuy*; then, break down the symbols and the four characters. The research includes the relationship between the stories and the beliefs and perspective at the time, in particular in 208 B.C when the second dynasty of Vietnam formed, and of the late 16th century Renaissance in England. Ultimately a comparison of the text, as well as extra-textual analysis, reveals that the ideas of ‘pure love’ exist well before the 20th century ‘Victorian’ period.

Context

In the Northern region during the semi-mythical Hong Bang period (2879 - 258BC), there were Au Viet tribes, living interspersedly with the Lac Viet people. At the end of the third century BC, Qin Shi Huang (founder of the Qin dynasty), sent his military in an attempt at dynastic expansion. Thuc Phan was elected as a general. After the victory, in 207 BC, Thuc Phan proclaimed himself as King An Duong Vuong, merged Au Viet and Lac Viet into Au Lac country, based his capital in Phong Khe, and built the Co Loa citadel (present-day Dong Anh, laying just outside of Hanoi, the current capital).

Though there have been several versions of the story of My Chau, the legend of *My Chau Trong Thuy* is said to exist in two books dating from the Tran Dynasty: *Dai Viet su luoc* and *An Nam Chi Luoc*. Later on, the story is found in *Linh Nam Chich Quai* - a book of legends and myths (Le, 2012). The date of this book is uncertain but is believed to have been compiled near the Le So Dynasty, most likely during the Ming Dynasty (1368 - 1644 AD).

Romeo and Juliet were not originally created by William Shakespeare. More than a century ago, in 1476, Italian author Masuccio Salernitano wrote a book *Il Novellino* about an affair, murders, and about a priest who helped to arrange the wedding of a young couple from two hostile families. William Shakespeare wrote the tragedy, *Romeo and Juliet*, in 1596. The play contains a message about the story of hatreds and conflicts occurring in the royal family, from King Henry VIII, Queen Mary Tudor, to Queen Elizabeth I, causing thousands of murders, bloody killings between factions of Catholics, and Protestants (Clunie).

An Duong Vuong was helped by the turtle god Kim Quy to build the Co Loa citadel. After the construction was completed, the turtle god gave him a claw to make a magic crossbow,

which had helped the king defeat the enemy in many fights, including ones with Nam Hai, the neighboring country. Refusing to lose, Trieu Da, king of Nam Hai, sent his son, Trong Thuy, to propose to My Chau—An Duong Vuong's daughter. Living together for a while, Trong Thuy inquired about the magic crossbow and had My Chau showed it to him. Knowing the secret, and using the excuse to visit his father, he switched the magic crossbow with an imitation one and brought the original back to Trieu Da. Trieu Da attacked Au Lac again. Because An Duong Vuong typically relied on the protection of the magical crossbow, he was not prepared. Losing the battle, the king rode his horse and brought My Chau forward to the sea. But wherever he went, the enemy followed. The king asked the god Kim Quy for help, and when he was enlightened that his daughter was the source of betrayal, he immediately drew his sword, killed My Chau, and jumped into the sea. When Trong Thuy discovered the body of his former wife, out of extreme pain he ended his life by jumping down a well.

Over fifteen hundred years later, in Verona, Italy, the Montague and Capulet families maintained a long-standing enmity. Romeo was the son of the Montague family, who fell in love with Juliet - the daughter of the Capulet family in the ball at the Capulet mansion. Against their families, the couple asked the priest Laurence to arrange a secret marriage for them. However, Juliet's cousin Tibal killed Romeo's best friend. To avenge his friend, Romeo stabbed Tibal to death and was banished and exiled. Juliet was then forced to marry Count Paris. She asked for help from priest Laurence. The priest faked her death for 24 hours by giving her a dose of sleeping pills. Then, he informed Romeo to come to the crypt to save her and escape together. But before the priest could explain the plan to Romeo, Romeo already heard of Juliet's death and fled in pain to Verona. On the way back, he bought poison to prepare for his suicide. At the cemetery, Romeo stabbed Paris to death and then drank the poison to commit suicide. As soon as Romeo died, Juliet's medicine wore off. She woke up and saw Romeo's body next to her, so she took a knife and killed herself.

Argument

After their meeting at the ball, both Romeo and Juliet were filled with grief. When their eyes met and their hearts were in sync, the two souls had belonged together. While they shared the same feeling for each other, their love was hindered by their families' feud. Therefore, in the

garden of Capulet's house, they lamented together under the moon. If only there were no barriers to hinder that love, perhaps Romeo could have been dignified in front of Juliet to express his feelings. With him, happiness and love were too fragile. Finding love was hard, keeping it was even harder. But Romeo's mood was rather simple. He fell in love and was willing to accept whatever the cost might be. As his feeling was reciprocated with love, as he felt her heart, he definitively affirmed his love by willingly giving up his family and his surname: "I take thee at thy word. Call me but love, and I'll be new baptized. Henceforth I never will be Romeo."; "My name, dear saint, is hateful to myself because it is an enemy to thee. Had I written it, I would have torn the world."

Romeo wanted to deny the hatred between the two families because they were enemies of love. Did the feud do anything other than bringing suffering? Facing Juliet's worry and torment not only for herself but also for her lover, Romeo's attitude was more drastic. He was ready to give up his family, showing the courage to sacrifice to love (Appelbaum, 1997). What Romeo feared was not winning the love of Juliet, the fear that she would look at him with hateful eyes: "There lies more peril in thine eye than twenty of their swords. Look thou but sweet, and I am proof against their enmity." For the heart that first felt the vibration, the moment he saw the eyes of his lover, all dogmatic morality became meaningless. He called his family "them" as they were strangers to him. Now, to him, Juliet is his life, "I have overcome this thanks to the wings of love."

Living in Au Lac following his father's sinister scheme, Trong Thuy did not marry My Chau for love, but for the purpose of using her to carry out a political plan entrusted by his father.. He took advantage of the gullibility of My Chau and deceived her to steal the magic crossbow. Before returning to his country, Trong Thuy asked My Chau how to find her to know where the king fled. It is these actions that directly caused the tragedy of a country and of a father and his daughter. He was the enemy of the Au Lac's people, a man who deserved to be condemned and eternally guilty. But regarding his special position, Trong Thuy had to shoulder tasks that cannot be granted to ordinary people. He 'had' to marry My Chau and 'had' to stay in the neighboring country to find a chance to steal the magic crossbow. Trong Thuy's situation and position are the basis for explaining his treacherous nature.

In contrast to Romeo, Juliet's mood is more thoughtful and cautious. After having met Romeo at the ball, Juliet went back to her room, stood by the window, overlooked the garden in the quiet night, and with the thought that there was no one around, she uttered her feelings out loud. Her words directly confessed her desirous love without any concealment of shame: "Or, if thou wilt not, be but sworn my love, and I'll no longer be a Capulet." Juliet's monologue represented tormenting anxiety, a torment expressing a troubled state of mind in the face of difficult circumstances. Juliet's monologues show that her love was burning. An exclamation phrase "Ay me" was used, but it not only showed the pent-up emotions that cannot be expressed in words, but it also contained a sign of anxiety, for two reasons: the hatred between the two families, the worry of whether Romeo really loves her (Brown, 1966).

And when she no longer thought about the Montague family, Juliet thought about her own Capulet family and asserted that the place where the two were talking was "the place of death" that "If they do see thee, they will murder thee." Juliet was aware of the walls separating their love: the stone wall of the garden, the wall of enmity between the two families that she did not know whether Romeo dared to overcome, and the wall of uncertainty about Romeo's true love. The inner development of Juliet is much more complex than Romeo's, but it is consistent with the psychology of the lover. The torment in her emotion shows the heavy pressure of the situation, the siege of the long-standing enmity between the two families, and the danger that threatened the two. This reflects both the maturity in her thinking and the passion in her emotion (Appelbaum, 1997).

My Chau, who was the daughter of An Duong Vuong, was a noble princess with a pure, gullible, innocent soul. She was the one who had to take great responsibility for the lost tragedy of her country. She was a beautiful and innocent princess, but had no sense of civic responsibility, political consciousness, and was only immersed in love and conjugal affection. My Chau was so naive and gullible that she arbitrarily used the national secret for her love, causing the treasures of the country to be swapped without her knowing, and only thinking of her personal happiness, she marked the way for Trong Thuy to chase. When evaluating this character, there have been many different opinions, critics, and advocates (Tran, 2015).

My Chau, in some perspectives, is criticized as the direct reason for the loss of the nation, however, we need to consider her role as a woman at the time (ibid). My Chau was a

mild-mannered girl who loves and commits to her husband with all her heart and mind; therefore, she is more pitiful than guilty. My Chau's action of showing Trong Thuy the magical crossbow and sprinkling the feathers illustrates the stereotypical emotional reaction of women. These actions stand for the love culture of Vietnam, which contrasts with the reasoning culture of the invaders (Le, 1966). However, not only was she a woman, but she was also a princess. And a princess who only knew how to fulfill the traditional role without caring about the fate of her country and her people is considered guilty (Tran, 2015).

The naivety of My Chau, the lie of Trong Thuy, the passion of Romeo, and the maturity of Juliet are influenced by the period of time that they were born. Coming from the feudal period when people had to endure the traditional perspective and judgment of other people, My Chau and Trong Thuy had to carry out their roles in the families or society. Regarding My Chau, she was judged in three ways: at home, she was subordinated to her father; after her marriage, she was subordinated to her husband; and after the husband's death, she had to follow her son (Tài gia tông phụ, xuất giá tông phụ, phu tử tông tử). This is the reasonable explanation for her complete reliability on her husband. As for Trong Thuy, his actions were very alert and decisive, so everything was completed to his plans. Stealing the magic crossbow, Trong Thuy and his father marched their troops to capture Co Loa. It was also his decisive and cold action that completely cut off Trong Thuy's emotional relationship with My Chau. In the role of a son and a prince, Trong Thuy had successfully completed the task assigned by the king, his father. But besides being a hero who has merits in expanding the country, Trong Thuy, as a husband, was a sinister, opportunistic man who was took advantage of his wife's feelings and beliefs to carry out plans for his benefit.

Regarding Romeo and Juliet, William Shakespeare was a typical author of European literature in the Renaissance period. Living in the transitional period from feudalism to capitalism, he quickly captured the breath and pulse of the times and incorporated them into his works. Therefore, Shakespeare's writing career is a reflection and criticism of both regimes. In his art, Shakespeare always spoke out in praise of people and demanded their right to life and to be free. His characters are new people of the new era, people who live with their hearts, who dare to raise their voices to express their aspirations, to overcome all hatreds and social ties (Cain, 1947). Romeo and Juliet represent such people. The Renaissance art movement, born

around the 15th century, awakened people's aspirations, promoting individuals, and affirming that people are the noblest. The ancient Greek philosopher: "Of all things the measure is Man", is the general idea of humanism in ancient Greek literature. It is also the main idea of Renaissance literature (UK Essays).

After the couple's tragic deaths, the two families erased the long-standing enmity. Eventually, they created a golden statue to honor and remember the love of Romeo and Juliet. At the end of the play, both Romeo and Juliet died but the freedom of their love remained forever. Because of his love for Juliet, Romeo did everything to make her happy (Applebaum, 1997). He crossed the high walls of the Capulet house, which also represents the grim darkness of medieval enmity. This long hatred is a cruel cut that weighs heavily down on the couple who were in love and ready to sacrifice. Their death, therefore, is a wake-up call for respect for the freedom of happiness and love. In a dark and cold circumstance, their passion and emotion warmed their love, brought breath and vitality to the soul as it is pure love.

Also, as a traditional part of Renaissance life, Romeo and Juliet's deaths were the result of unresolved contradictions of the times. In other words, to deal with the conflict, Shakespeare came up with a solution to sacrifice his ideal characters, because contemporary social evils such as family feuds were not easy to erase. Therefore, he was forced to borrow the death of the couple to "kill" a legacy of medieval feudalism (N.T.M.L, 2006). The sacrifice of two people changed the hatred between the two families as a result of their grief for the passionate love. And the statue has partly made their dream of being together a reality. Moreover, the deaths of Romeo and Juliet marked the triumph of the humanist ideal.

My Chau committed an unforgivable sin as a citizen of a country and died by her father's sword. My Chau has paid for her guilt, her justice needed to be dissolved. Her actions were unintended. When she heard the judgment of Kim Quy god, she did not pray for pardon but begged to be forgiven for her blunder: "If I had intended treason and plotted against my father, I would be turned into dust when I died. If I was fooled because of my loyalty, I would die becoming pearls to clear the feud." As the sword of the father swung, the blood of the girl flowed into the ocean and the shellfish which ate it changed into pearls. Her words became reality, and the injustice is vanquished.

As for Trong Thuy, in the wake of the death of My Chau, he suffered in regret, and as a result, jumped down the well to commit suicide. The image of the well is also a mirror reflecting the sins of Trong Thuy. And that he gave up his throne and wealth to jump into the well allows us to infer his repentance, grace, and above all, his love for his wife despite having remained loyal also to his father. Trong Thuy is the essential son of filial piety.

According to legend, when people wash the pearls with water from that well, the more they wash, the brighter the pearls become. Through that detail, the hatred in My Chau's heart is believed to have been resolved. In their previous lives, My Chau and Trong Thuy were two unfortunate people in two different worlds, but they got caught up in that cycle of love and then fell into tragedy. But in the end, no one was worth blaming, as those two miserable people had to carry their responsibility. In this life, they had paid enough, so they died with the hope that in the other life, they can live together, without any resentment. Additionally, My Chau and Trong Thuy's death raises a warning to the reality of wars, reflecting the relationship between the destiny of nations and the happiness of individuals.

At first glance, the deaths in Romeo and Juliet and the deaths in My Chau Trong Thuy appear completely different: one is voluntary in the face of forbidden love, the other is approved but intentional, but the two loves result in the same ending: their deaths. But they did not die meaninglessly. They died to clear the animosity between the two families and above all, to prove their extraordinary love and their willingness to sacrifice for their lovers. From these tragedies, which come from two different cultures, we see that romantic love between humans appears in any land and any period of time. Perhaps there is nothing that can hold back this kind of emotion as it can bring the purest, innocent yet powerful feeling that has the ability to break long-standing feuds. The love between humans is unrestrainable and therefore, in both cultures, love is featured and appreciated. Through the stories, the statement that it is everyone's right to pursue their love and happiness without any restrictions and prohibitions is proclaimed.

Limitations of the research

This research has to be seen in light of some limitations. First, the research only lasts for two months. As a result, to meet the deadline, this paper can not include every perspective and

theory. Second, in *Romeo and Juliet*, only two scenes of the stories were included. As the goal of the research is to point out the cultural impacts through the similarities and differences between the stories, this paper focused narrowly on certain parts of the text.

Some scholars may disagree with the pure love of Romeo and Juliet and argue that their love is a selfish one. Their actions were based on their own will and what they thought was the best. At that time, their love had a great impact on their families' names. What would people think when Capulet's daughter married their enemy's son? Therefore, it was one of Romeo and Juliet's responsibilities to maintain the reputation of their family.

Conclusion

As seen in the comparison between *Romeo and Juliet* and *My Chau Trong Thuy*. By comparing certain scenes: the moonlit night, the characters, and the circumstances of their deaths, this study showed that even when *Romeo and Juliet* and *My Chau Trong Thuy* come from distinct cultures and periods of time, they share similarities in terms of plot, and moral lessons. However, the two tales are different in terms of the attitudes of the characters towards love and the motivations behind their actions. This contrast is explained by the cultures themselves, the period that the stories were born of and the perspective they are influenced by. Stories play an important part in fulfilling spiritual needs for people in the modern world. Therefore, future research into how cultures shape stories should be carried out to draw a clearer picture of the connection between culture and literature.

References

- Appelbaum, Robert. "‘Standing to the Wall’: The Pressures of Masculinity in *Romeo and Juliet*." *Shakespeare Quarterly*, vol. 48, no. 3, 1997, pp. 251–272. *JSTOR*.
- Brown, Carolyn E. "Juliet's Taming of Romeo." *Studies in English Literature, 1500-1900*, vol. 36, no. 2, 1996, pp. 333–355.
- Communications MDR. *Environmental Scan of the Culture Sector: Ontario Culture Strategy Background Document*, Apr. 2016, p. 6.
- Christine K., Helen. *Literature preserves Papua New Guinea (PNG) cultural heritage*, 2012, <http://www.pngbuai.com/800literature/heritage/png-literature-heritage.pdf>.
- Clunie, Aurelia. "Religion in Elizabethan England." *Hartford Stage*, <https://www.hartfordstage.org/stagenotes/hamlet/elizabethan-era/>.
- Cain, H. Edward. "'ROMEO AND JULIET': A REINTERPRETATION." *The Shakespeare Association Bulletin*, vol. 22, no. 4, 1947, pp. 163–192.
- Clark, Glenn. "The Civil Mutinies of 'Romeo and Juliet.'" *English Literary Renaissance*, vol. 41, no. 2, 2011, pp. 280–300.
- Dundes, Alan. "Folklore as a Mirror of Culture." *Elementary English*, vol. 46, no. 4, 1969, pp. 471–482.
- Francisco, . "Difference Between Fairies Tales and FolkTales." *Difference Between Similar Terms and Objects*, 22 May. 2017, <http://www.differencebetween.net/miscellaneous/culture-miscellaneous/difference-between-fairies- Tales-and-folk-tales/>.
- "How is Hamlet Character Influenced by Greek Philosophy?." *UKEssays*, 4 Sep. 2017, <https://www.ukessays.com/essays/english-literature/hamlet-character-influenced-greek-7592.php?vref=1>.
- Kuli, C. Helen. *Literature preserves Papua New Guinea (PNG) cultural heritage*, 2012, <http://www.pngbuai.com/800literature/heritage/png-literature-heritage.pdf>.

- Khan, Coppélia. "Coming of Age in Verona." *Modern Language Studies*, vol. 8, no. 1, 1977, pp. 5–22.
- La, N. Thin, et al. "Truyen An Duong Vuong va My Chau - Trong Thuy" *Ngu Van 10 Tap Mot*, vol.1, 4th ed. *Ministry of Education*.
- Loske, Alexandra, and Robert Massey. *Moon: Art, Science and Culture*, 2018
- Little, William. "Culture." *Introduction to Sociology – 1st Canadian Edition*, chap. 3, opentextbc.ca/introductiontosociology/chapter/chapter3-culture/.
- Le,Hao. *Di tim An Duong Vuong, My Chau, Trong Thuy: tu lich su den truyen thuyet*, 1966.
- Le, Phuoc. "Trong Thuy - My Chau va bai hoc canh giac xam luoc." *Tap chi Van Hoa*, 2012, <https://www.rfi.fr/vi/viet-nam/20120914-trong-thuy-my-chau-va-bai-hoc-canh-giac-truoc-ke-thu-xam-luoc>.
- Nguyen, T. Long, and Vu Hong Van. *Ancestor Worshiping Beliefs in the Beliefs and Religion Life of Vietnamese People: Nature, Values, and Changes of It in the Current Period*. Aug 22. 2020.
- Nguyen, Thai. "My Chau & Trong Thuy, 2016." *National Fine Arts Publisher*, 2016.
- N.T.M.L. "Romeo and Juliet - "Thuong hieu" cua tinh yeu." *Song Huong*, Jan 2006, <http://tapchisonghuong.com.vn/tap-chi/c124/n1112/Romeo-and-Juliet-Thuong-hieu-cua-tinh-yeu.html>.
- QuackieHels. "Romeo & Juliet - Why Is Cosmic and Celestial Imagery Used in Act 2, Scene 2?." *StudyModeResearch*, Feb 11. 2013, <https://www.studymode.com/essays/Romeo-Juliet-Why-Is-1418240.html>.
- Shakespeare, William. "Romeo and Juliet, 1597." *Oxford: published for the Malone Society by Oxford University Press*, 2020.
- Stearns, Peter N., and Mark Knapp. "Men and Romantic Love: Pinpointing a 20th-Century Change." *Journal of Social History*, vol. 26, no. 4, Oxford University Press, 1993, pp. 769–95, <http://www.jstor.org/stable/378878>

Theory X and Theory Y: McGregor's Theories of Management Applied to Working from Home in the Era of COVID-19 by Daniel Youssef

Abstract

Now more than ever, employers need to know how to effectively manage and motivate their employees -- especially in light of the COVID-19 pandemic, which has presented a diverse set of new challenges, including the transition to working from home. Theory X and Theory Y are prominent theories of management as it relates to motivating employees. A deeper view into these theories will be provided using self-determination theory (SDT). This paradigm is applied to determine when one theory is better than the other when managing employees during the COVID-19 pandemic, especially those who are working from home. In previous studies, researchers believed that Theory Y was more effective, as Theory X can cause friction in the workplace in an organization that relies on authoritarian management. However, in contrast to researchers' assumptions that Theory Y is always a more appropriate method, using the framework of SDT, scenarios will be proposed in which one theory would be better utilized than the other, as supported by previous research.

Keywords: Theory X and Theory Y, self-determination theory, psychology, management, working from home

Introduction

When the COVID-19 pandemic broke out, numerous facets of life were affected, including business practices. One of the most salient changes is the adjustment from in-person to remote work. As working from home continues to become more prevalent, employers must be able to effectively manage their employees. Theory X and Theory Y are two management styles, developed by Douglas McGregor, which dictate the appropriate management method based on assumptions about employees. Theory X states that employees do not like to work and must be influenced into working via external rewards, and in some cases, punishments. Theory Y states that employees enjoy working and are motivated to do so, and, as such, employers should take a less controlling approach in their management style. This allows employees the flexibility to pursue their goals. In this paper, self-determination theory (SDT), a theory of self-motivation, is incorporated into Theories X and Y, enriching researchers' knowledge of these theories. With this framework, propositions will be created and applied to scenarios in which employees are working from home.

Review of Literature

Theory X and Theory Y, which were developed by Douglas McGregor, a professor of management at the Massachusetts Institute of Technology, are based on the belief that managers make assumptions about the attitudes and behaviors of their employees (Gannon, 2013). Theory X assumes that employees are lazy and work solely for money or other extrinsic rewards. As such, they must be coerced into working via those extrinsic rewards. Theory X also prescribes that punishments have the same effect. In contrast, Theory Y assumes that employees enjoy working and need no external rewards or close supervision to be motivated to do so. Thus, employers take a less controlling approach in their management style. This allows employees the freedom to accomplish their goals in the way that most motivates them and optimizes the enjoyment of their work. In determining when to use which method, researchers have considered a variety of factors, most of which are encapsulated in the demographics of employees and/or the industry in which they work.

Demographics

Researchers have considered the demographics of employees, more specifically their age and gender, as factors in the use of Theory X or Theory Y. Results do not support this. Marjan Bojadziev et al. (2016) conducted a study at the University American College Skopje and found that, regardless of age, employees preferred Theory Y, causing high levels of intrinsic motivation and satisfaction with their organization. Conversely, Elen Navasardyan of the American University of Armenia conducted a study that determined that, notwithstanding gender, employees have higher levels of extrinsic motivation than intrinsic motivation, indicating a preference for Theory X management (Navasardyan, 2018). Thus, age and gender do not seem to play a significant role in the preferred management style of employees. However, while both studies indicate a preference for one style for all employees, both studies reach different conclusions in terms of preferred management style.

Industry

Since preferences for Theory X and Y are not universal, the industries in which employees work may also influence their preferred management style. In the business process outsourcing (BPO) industry in the Philippines, employees were found to prefer Theory X (Delle-Vergini, 2018). In one study of the retail industry in Ireland, employees at an Irish retail company were found to be best motivated with external, financial incentives, a key motivator found in Theory X management (Keogh, 2011). Another study in 2020, which examined employees at the Calvin Klein outlets, reached the same conclusion: employees were found to be better motivated with monetary rewards (Lahtinen, 2020). In a 2018 study conducted by the University of Central Florida, researchers examined multiple public sector organizations to determine their preferred method of management. Employees' preferences for a certain method differed based on the organization. In organizations that utilize authoritarian management, such as the Department of Motor Vehicles and the Fire Department, Theory X was the preferred management style. Other departments, however, such as the Department of Parks and Recreation and Arts Department, prefer Theory Y. In school systems, employees seem to prefer Theory Y management. In a 1993 study of Chicago public schools, school staff overwhelmingly preferred principals who utilized Y-management rather than X-management, especially those in

elementary and secondary schools (Gillman, 1993). As such, the type of industry in which employees work likely affects their preferred management style.

As in the case of age and gender, these results are not always consistent, and they sometimes differ from the expectations of researchers (Aykut, 2019). There does not appear to be an underlying framework for when to use one management theory over the other. A framework, based on self-determination theory, will be offered, contributing to this literature.

Theoretical Framework

Self-Determination Theory (SDT) is a theory of motivation that focuses on human behavior, motivated by the fulfillment of psychological needs (Deci & Ryan, 2000). It posits that people have three fundamental psychological needs related to self-actualization: autonomy, competence, and relatedness (Deci & Ryan, 2000). Autonomy is the feeling of free will. Competence is the need to learn skills. Relatedness is the sense of belonging with others. This paradigm places motivation within the bounds of self-actualization and the three needs. Intrinsic motivation is self-motivation, caused when the individual finds enjoyment in the activity itself and is therefore motivated to complete it. For people who are extrinsically motivated, external influences like rewards and punishments are necessary. Theory X's assumptions about employees parallel those of employees that are extrinsically motivated, as both types of employees are motivated by extrinsic rewards, and Theory Y's assumptions parallel those of intrinsically motivated employees. Thus, the tenets of SDT and the determinants of motivation in SDT can be used to predict whether people behave like the assumed employees in Theory X or Y, and therefore, the best management style for a given situation. X-management is better suited for employees who are extrinsically motivated, while Y-management is better for those who are intrinsically motivated.

Researchers have assumed that Theory Y is invariably a better management style. For example, in a study conducted by Linnaeus University, the researchers hypothesized that female employees would have higher job satisfaction under Y-management. The data did not support the hypothesis (Aykut, 2019). Bojadziev et al. (2016) also assumed that Theory Y was a superior management method, but this was not always the case. Despite these inconsistencies, researchers have not provided a predictive framework to determine when and why Theory X could serve as a

more effective management style. Using the provided framework, propositions will be created to explain this discrepancy and help researchers determine when one style would be better utilized.

Propositions

Proposition 1: According to Self-Determination Theory, the extent to which a behavior is intrinsically motivated depends on the extent to which the activity fulfills one's psychological needs (Deci & Ryan, 2000). As an employee's motivation determines whether they would optimally respond to Theory X or Theory Y, the extent to which an employee's psychological needs are fulfilled determines which theory to utilize. This would explain some of the inconsistent findings mentioned in the previous section. In the study of the BPO industry in the Philippines, it was found that employees preferred Theory X. This may not be correlated with the industry in particular, as the Philippines and many other countries in the region have an organizational culture of hierarchical management (Delle-Vergini, 2018). In the Fire Department example, the department runs on strict guidelines with a rigid organizational structure akin to the military. Employees are allowed very little autonomy and there is scarce room for creativity in such a job. Other departments, however, such as the Department of Parks and Recreation and Arts Department, rely on creativity to come up with new ideas and advance their work. This creativity can only be achieved when allowed to do so under a Theory Y structure, as Theory Y is associated with higher levels of creativity. Therefore, the extent to which employees can satisfy their basic psychological needs influences their intrinsic motivation. As such, employees who cannot fulfill their needs of autonomy, competence, and relatedness at work will respond better to Theory X. Formally:

According to SDT, the extent to which the basic needs are fulfilled determines whether or not an employee is intrinsically motivated. However, need fulfillment should only be related to intrinsic motivation if the employee associates need fulfillment with work (Pacesila, 2020). This provides a moderator for Proposition 1. Since motivation affects whether employees will be influenced by Theory X or Theory Y, fulfillment of needs should only affect whether X or Y should be used if fulfillment is directly related to work. While employees who are working remotely are not intrinsically motivated by the tasks they perform, they still associate work with the fulfillment of their needs. Thus, the implementation of work programs to fulfill needs will shift the preference to Theory Y. Formally:

P2: Need fulfillment leads to a preference for Theory Y management, to the extent that need fulfillment is associated with work.

These propositions will be applied to an area of management that has gained new prominence since the start of the COVID-19 pandemic: working from home.

Application

The framework in integrating SDT with Theory X and Theory Y can be applied to working from home, which has become increasingly common in recent years, and has increased in popularity during the pandemic. Before the pandemic, 17% of employees in the United States were working from home; this increased to 44% during the pandemic (Mlitz, 2020).

The Influence of Remote Work on Need Fulfillment

There are numerous differences between in-person and remote work that affect need fulfillment.

When employees work from home, they are surrounded by objects that distract them. If an employee who is working remotely chooses to ignore the aforementioned distractions and focus on their work, they can achieve a sense of autonomy. In a physical workplace, however, these distractions do not exist, or are at least minimized, so that feeling of autonomy cannot be achieved.

In many, although not all, remote work settings, programs that can help employees learn new skills for their job, such as career advancement programs, are not available. Without such programs, employees may believe that they are not learning all the skills they need to best complete their work, and thus, they may not achieve the psychological need of competence.

In an in-person setting, employees can satisfy their need for relatedness through camaraderie with coworkers. However, in a remote workplace, employees are more distant from their coworkers, and the fact that any interactions are virtual may mean that they cannot satisfy the need for relatedness in the way they could while working in-person. As such, employees might not be able to fulfill their need for relatedness when working remotely, at least by current practices.

Framework Recommendations

The influence of remote versus in-person work on need fulfillment has been discussed, which is the foundation of both propositions. Therefore, recommendations based on those influences will be proposed:

Per Proposition 1, the extent to which one's needs are fulfilled would determine whether to use Theory X or Theory Y. However, some of the basic psychological needs may be enhanced by working from home, while others are diminished. To determine the net effect, managers must understand the type of employees they have. If they are extraverted, they may place more emphasis on relatedness for need fulfillment. If they are Type A personalities, they may achieve optimum motivation by being allowed to manage themselves; therefore, they may place more emphasis on autonomy for need fulfillment. The former, then, would be motivated by external rewards and punishments, while the latter would strive for need fulfillment and prefer Theory Y.

Even if employees feel their needs are not currently being fulfilled, companies have tools to help fulfill them. For example, if employees are not able to fulfill their need for relatedness, but their organization cannot impose a Theory Y structure, employers can bolster relatedness through events such as virtual happy hour, etc. They can also try sending surveys to employees, prompting them to submit ideas on how employees can better connect with each other. This strategy may be better incorporated into a Theory Y structure.

Per Proposition 2, need fulfillment can lead to greater intrinsic motivation and Theory Y use if need fulfillment is specifically associated with work. Companies have several options that they can consider to more intimately connect certain fulfillment areas with the office. Since employees associate work with need fulfillment, companies can change the way they describe events to better increase employee turnout and satisfaction; this may take the course of, for example, renaming "virtual happy hour" to "company-sponsored virtual happy hour." Companies can also provide scholarships for employees looking to continue their education. These could be called "company skill scholarships." These changes may cause employees to attribute their need fulfillment to the company. As a final example, a company-sponsored mindfulness program, which emphasizes greater focus and fewer distractions, may have employees attributing their increased autonomy (because they are not distracted at home) to the company, rather than to themselves, increasing the likelihood that they would benefit from Theory Y management.

Future Research

The researcher has found limited literature on the relationship between the basic psychological needs and remote work. Also, subsequent research could focus on other factors that may influence an employees' preferred management style, such as their personality, the status of employees' upcoming projects, and company culture.

Conclusion

In light of the COVID-19 pandemic, managers must be able to effectively manage their employees -- who are working from home in greater numbers than ever before -- using Theory X and Theory Y. Although Theories X and Y have been prominent management theories since their inception in the 1950s, no guidelines were available to help managers determine which style of management to utilize, and when. A second theory of motivation, self-determination theory, was integrated to develop a framework, from which several novel propositions were developed as to when one theory is superior to the other. The propositions were applied to working from home. These propositions also help explain inconsistencies in previous research.

Acknowledgments

I would like to thank my family for their constant support throughout this project. I would also like to thank Andrew Smith, my mentor, for his invaluable guidance and feedback.

Author

Daniel Youssef is a senior at the Advanced Math and Science Academy Charter School in Marlborough, MA. He is passionate about psychology and business, which he plans to study in college.

References

- Aykut, H. M. (2019). The Relationship Between Theory X/Y Management Styles and Job Satisfaction: Moderation Roles of Self-Efficacy and Gender.
- Bojadziev, M., Stefanovska-Petkovska, M., Handziski, V., & Barlakoska, G. (2016). Age related preferences of leadership style: testing McGregor's Theory X and Y. *Journal of Management Research*, 8(4), 187-207.
- Deci, E. L., & Ryan, R. M. (2000). The "what" and "why" of goal pursuits: Human needs and the self-determination of behavior. *Psychological inquiry*, 11(4), 227-268.
- Delle-Vergini, S. (2018). Missing in Action: Implications for the management of employees working from home in the Philippines' BPO industry.
- Gannon, D., & Boguszak, A. (2013). Douglas McGregor's theory x and theory y. *CRIS-Bulletin of the Centre for Research and Interdisciplinary Study*, 2, 85-93.
- Gillman, L. S. (1993). *Staff satisfaction and leadership behavior of Theory X-and Theory Y-oriented principals in the greater Chicago public school system* (Doctoral dissertation, Andrews University).
- Johnson, J., Irizarry, M., Nguyen, N., & Maloney, P. (2018). Part 1: Foundational theories of human motivation.
- Lahtinen, E. (2020). Employee Motivation and Incentives in Retail Business: Case Company Calvin Klein Outlet.
- Mlitz, K. (2021, April 9). *Remote work frequency before/after covid-19 2020*. Statista. <https://www.statista.com/statistics/1122987/change-in-remote-work-trends-after-covid-in-usa/>.
- Navasardyan, E. (2018). *Motivational factors in driving employee performance* (Doctoral dissertation).
- Pacesila, M., & Colesca, S. E. Motivation Of Human Resources: Perceptions And Trends.

Slattery Keogh, L. (2011). *An exploration of motivation and psychological contract issues amongst employees and managers within the retail sector in Ireland* (Doctoral dissertation, Dublin, National College of Ireland).

**The Future of Youth Voter Participation:
A Call for States to Revamp Voter Registration Methods by Charlie Selbin**

Introduction

Section 1 of the 26th Amendment provides: “The right of citizens of the United States, who are eighteen years of age or older, to vote shall not be denied or abridged by the United States or by any State on account of age.” (U.S. Const. amend. XXVI, § 1.) Unfortunately, a large percentage of the population does not take advantage of this right, and young people in particular are under-represented in the voting population. Census data suggests that the primary reason for this under-representation may be a failure of young voters to register: in 2020, eighteen to twenty-four-year-old citizens (referred to in this paper as “young voters”) who registered to vote actually voted at fairly comparable rates as citizens over the age of twenty-four (referred to in this paper as “older voters”), but they registered in much lower numbers. Specifically, in 2020, 86% of registered young voters voted, but only 60% were registered. By comparison, 92% of registered older voters voted, and 74% were registered. So while there was only a six point differential between the two groups in terms of voting by those registered, there was a fourteen point differential in registration. (*Voting and Registration in the Election of November 2020*) This is an improvement compared to 2016, when there was a seventeen point differential in registration: 78% of registered young voters voted, but only 55% were registered; by comparison, 88% of registered older voters voted, and 72% were registered. (*Voting and Registration in the Election of November 2016*)

This and other data strongly suggests that one key to increasing young voter participation may be simply to increase their registration. Therefore, all 50 states should implement and expand pre-registration and automatic voter registration (AVR) by enacting laws: 1) allowing sixteen to eighteen-year-olds to automatically pre-register to vote, 2) implementing or expanding access to AVR through government agencies, 3) permitting and incentivizing large companies to register all employees and offer registration to customers, and 4) encouraging and incentivizing high schools to offer pre-registration.

Barriers to Young Voter Participation

Young voters face significant barriers to participation which, although not unique to their demographic, are fairly widespread among them. Unfortunately, as political scientists D. Sunshine Hillygus and John B. Holbein observed, young people are less likely to follow through on good intentions, including the intent to vote, when they are presented with obstacles. (*Making Young Voters: Converting Civic Attitudes into Civic Action* 14) And the reality is that young people face many obstacles to voting including the following: registration problems, lack of transportation, restrictive voter ID requirements and inflexible schedules. A 2018 study by the Center for Information & Research on Civic Learning and Engagement (*Why Youth Don't Vote*) at Tufts, while focused on differences correlated to race and education (which will not be examined here), identified several obstacles shared by young voters generally. (*IBID.*)

First, the CIRCLE study found that 20% of all young people—regardless of college status—cited “registration problems” as a factor in why they did not vote. (*IBID.*) One possible explanation for why students who do not attend college fail to register is that they lack the peer motivation or support from school student organizations. As a result, they may not pursue registration if they do not know their social security number or do not understand the registration form. College students may face their own barriers for registering by being “out of district” during elections, meaning that they may have registered in their home district and are in a new district while away at school. Conversely, students who change their registration to the district in which their college is located may find themselves at home during an election, as happened to many students during the Covid-19 pandemic, and as often happens when students move to a new district for graduate school or a first job out of school. (Gray)

A second barrier faced by many young voters is lack of transportation to voting precincts, particularly in states that have reduced the number of voting locations. The CIRCLE study found that 29% of all young voters (35% of non-college students and 19% of college students) cited lack of transportation as a reason they did not vote. (*Why Youth Don't Vote*) In recent years, there have been both governmental and non-governmental efforts to address this problem, by, for example, ensuring there are polling places on campus and offering free rides (through companies like Uber) to off-campus polling places. (Gurley; Douglass; Cobler)

A third obstacle is that ever more restrictive voter ID requirements (cited by 21% of young voters in the CIRCLE study) may limit the ability of college students to vote in the state

where they attend college. (*Why Youth Don't Vote*) The CIRCLE study suggests that young voters in college are particularly apt to identify this issue as a barrier to registration because of the effort in many states to disallow use of a college ID as a valid form of voter identification. (*IBID.*)

Finally, young voters who are working full-time are almost always new employees, making it difficult to leave work to vote if the employer does not provide paid time off. The CIRCLE study found that approximately 45% of all young voters cited being too busy (presumably because of classes or a job) as a reason they failed to vote. (*IBID.*) As of now, not all states mandate that employers provide employees paid time off to vote; many only allow one or two hours off, which may not be sufficient if voting lines are long, and those states that do mandate time off often allow only unpaid leave. (*State Laws on Voting Rights*)

Overcoming the Barriers: Expanding Pre-Registration and AVR

While these obstacles are daunting, it is also true that voting is a habitual behavior, meaning that doing so once increases the likelihood of doing it again; getting young people to register and vote as early as possible is essential to promoting future engagement. As Joshua Harder and psychologist Jon A. Krosnick assert, voting can be “self-reinforcing, meaning that the social and psychic rewards one enjoys after voting once may be memorable and motivating at the times of subsequent elections.” (537) They continue, “by voting once, a voter might realize the ease of doing it and may therefore be less inhibited from doing it again.” (*IBID.*)

For teens, who are particularly susceptible to peer influence, the lack of peer reinforcement results in a failure to establish good voting habits. (Plutzer 42) It is reasonable to speculate that the opposite would also be true: as more young voters model good civic habits for one another by registering to vote and going to the polls, they can reinforce good voting habits among their peers, and a greater percentage of young people will vote. If we can remove the most significant barriers to participation, allowing young people to get their first voting experience behind them as early as possible, then youth voter participation should significantly increase.

One way to almost certainly (although not inevitably) increase youth participation is to introduce pre-registration and AVR laws in every state. Pre-registration means registering citizens to vote before they are old enough to be eligible, so that when they turn 18, they are already registered to vote. AVR is the act of registering citizens to vote through their interaction

with regular government business. AVR means that (1) any individual who interacts with the institution or business becomes registered unless they opt out and (2) the identifying information individuals provide to the institution or business is transmitted to election officials who verify their eligibility to vote, allowing a seamless and secure process. (Morris and Dunphy 1)

AVR can be accomplished through several means. Currently, AVR typically happens through a state's driver's license offices and is often a combination of automatic registration and pre-registration: upon obtaining a license, the individual becomes automatically registered if over 18 and pre-registered if under 18, with states implementing different methods to allow the DMV license applicant to opt out of registration. (*Automatic Voter Registration*) As of January 2021, twenty-one states and the District of Columbia permit some form of AVR, typically through the DMV (Alaska does so through its annual check mailed to more than 90% of residents participating in its Permanent Fund Dividend linked to the state's oil revenue). (*Automatic Voter Registration*; Morris and Dunphy) In theory, a voter could be automatically registered through schools or a non-governmental agency, such as an employer, large retailer, or insurance company, but to date, no such alternative automatic registration has been implemented.

The Brennan Center for Justice conducted a comprehensive multi-state analysis of AVR to determine its effectiveness and found that AVR increases registration between 9 and 94%. (Morris and Dunphy, 1) Furthermore, the increases can be found in large and small states and in states across the political spectrum, and the increases are similar regardless of how the states implement the opt out option (most states provide the option at the first point of contact with the government agency, but some states provide the option later). (1, 2) The Brennan Center rightly points out, though, that in states where car ownership is relatively low, or where the state requires very infrequent visits to the DMV, the impact of AVR through the DMV will be relatively small when compared to other states, and it might well make sense to implement AVR at other government agencies. (16) The Brennan Center analysis is particularly rigorous because, unlike previous studies that simply looked at increases in registration after the implementation of AVR, the Brennan Center used the matching method to match areas that implemented AVR with demographically similar areas that did not implement AVR in order to control variables and determine the registration differential likely attributable to AVR. (2, 6)

One noteworthy state is Georgia, where the Brennan Center found a nearly 94% increase in registration due to AVR. (9) At present, 95% of eligible Georgia citizens over 18 are registered

to vote, one of the highest registration rates in the country. (Niese) Although the Brennan Center concedes that the reasons for the increase are outside the scope of its report, the results are so staggering and such an outlier from the rest of the nation that only regional voting rights initiatives can explain the difference. The high-profile campaigns of Senators Warnock and Ossoff, as well as Stacey Abrams' well-documented efforts, undeniably played a significant role in increasing turnout. However, a comprehensive 2020 election administration and voting report indicated that much of the increase in registration can actually be credited to Brian Kemp, who defeated Abrams in the 2018 governor's race (an ironic finding since, according to Abrams, he subsequently instituted extensive voter suppression tactics). (Velasquez) In 2016, Kemp, then Secretary of State, implemented AVR through the DMV, and, according to the report, voters enrolled through AVR now make up at least 67% of total registered voters in Georgia. (*IBID.*)

The Brennan Center's findings for Oregon indicate the limits on the impact of AVR, specifically in closed primary jurisdictions. If registration is automatic, there must be an additional step, at some point in the process, for a voter to indicate party affiliation; if that step is not taken, the voter will be deemed nonaffiliated and will not be eligible to vote in a primary. (Morris and Dunphy 4,8) In Oregon, voters must return a postcard to indicate their party affiliation. (*IBID.*) Although registration rates due to AVR increased by nearly 16%, only 14.5% of people registered through AVR in 2018 returned the postcard to select their party. To help overcome this additional barrier to voting participation, the DMV could generate a reminder text to all registered but non-affiliated voters every month until they return that postcard. Once the postcard was returned with the selected party, these reminders would end. One possible problem is that spam texts are so commonplace that the DMV texts might be ignored, and older voters who do not text might never see them.

The success of AVR and pre-registration is consistent with the findings of a Pew Charitable Trust report on the reasons people fail to register. According to the Pew report, the second most common explanation that respondents gave for why they had not registered—given by 27% of those polled—was that they had intended to register but had not gotten around to it. (Creek and Ueyama 3) Furthermore, more than 60% of the adult citizens surveyed said that they had never been asked to register. (2) Given how many people intend to register and how rarely people are provided with a simple opportunity to do so, it is reasonable to conclude that if AVR and pre-registration laws were put into place in every state, registration rates would increase

significantly. States could automatically register anyone eighteen or older and increase youth voter participation by ensuring that anyone sixteen or seventeen would be automatically pre-registered to vote while engaging in other regularly performed activities; that pre-registration would then be automatically converted to an actual voter registration at age eighteen, making it easier for young citizens to vote early and establish good voter participation habits.

Strategies for State Implementation of Pre-Registration and AVR

The extent to which youth voting would increase even with nationwide pre-registration and AVR remains an open question, since it is possible that many of the young people who will be most likely to vote are the ones who already make the effort to register. That said, given the research findings about obstacles to youth voter participation discussed above, it is reasonable to conclude that youth voting would substantially increase with widespread pre-registration and AVR.

If all states were on board with pre-registration and AVR, the question still remains as to how this process would be executed. One obvious method is through the expansion of AVR to every state's Department of Motor Vehicles, so that anyone who acquires a driver's permit or license would automatically be pre-registered to vote. On or around the time most teenagers turn sixteen, they are likely to go to the DMV to get a driver's license, and could be automatically pre-registered there. Without pre-registration, DMV-based AVR would be less effective, since it could be many years before a sixteen or seventeen-year-old returns to the DMV. Pre-registration, therefore, can be the gateway for young people to get involved in voting because it removes a barrier to participation and could be an important factor in increasing future young voter turnout. (Holbein and Hillygus, *Making Young Voters: The Impact of Preregistration on Youth Turnout* 366)

Not every sixteen or seventeen-year-old obtains a permit or license, so states should identify other places where people can pre-register or automatically register on a large scale with little to no effort. (Gross) Some obvious options include libraries and schools; each state could incentivize high schools to offer pre-registration, with a front-end opt-in via parental signature. Although, pursuant to the Family Educational Rights and Privacy Act (FERPA), schools cannot disclose student information without authorization, this opt-in process would ensure the necessary authorization. (20 U.S.C. § 1232g; 34 CFR Part 99) In addition, the IRS may be a

viable option, since 90% of Americans appear on a tax return each year. (Bearer-Friend and Williamson)

Since AVR won't register everyone, registration should also be encouraged elsewhere. Employers could be incentivized to help their employees register to vote, by, for example, including voter registration forms with the other forms new employees fill out. If even just Amazon and Walmart were to automatically register every employee they hired in the United States, they could potentially register approximately 2,500,000 people. (Reuter) And, if just fast food chains—some of the largest employers of young people—were encouraged to register all of their employees, between 3,500,000 and 4,000,000 people could become registered to vote. (Huddleston) The major insurance companies, who cover such a large number of Americans, could offer the same registration option to anyone who purchased insurance.

Conclusion

While young voters are under-represented in the voting population, a significant portion of that difference is attributable to the under-registration of young voters in the first instance, as well as obstacles to young voter participation. These obstacles are significant, and include few opportunities for registration, a mis-match between place of registration and place of residence, lack of transportation, ever more restrictive voter ID requirements, and inflexible schedules. Evidence suggests that automatic pre-registration (for those under age eighteen) and AVR (for those eighteen and older) would make a significant dent in this problem. That said, AVR will have a relatively low impact on registration in states where car ownership rates are low or where only infrequent visits to the DMV are required, and in closed primary states, since the voter must take the affirmative step of choosing a party (in closed primary states, automated texts to the registered voter until a party has been selected should help). For states that fall into any of these categories, voters should be automatically registered at other government agencies and other entities that interact administratively with a large percentage of the population, including schools, insurance companies, and employers who hire a large number of young people.

Undertaking these practical steps to increase registration of young voters and thereby cultivate good voting habits may well transform the 26th Amendment's "thin paper" promise of the right to vote into the "thick action" of young voter participation in our democracy.

References

- King, Martin Luther, Jr., “The Montgomery Bus Boycott” (speech, Montgomery, Alabama, December 5, 1955), BlackPast, <https://www.blackpast.org/african-american-history/1955-martin-luther-king-jr-montgomery-bus-boycott/>
- The Constitution of the United States: A Transcription*. National Archives, U.S. National Archives and Records Administration, 4 May 2020, www.archives.gov/founding-docs/constitution-transcript.
- US Census Bureau, “Voting and Registration in the Election of November 2020,” The United States Census Bureau, July 27, 2021, <https://www.census.gov/data/tables/time-series/demo/voting-and-registration/p20-585.html>
- US Census Bureau, “Voting and Registration in the Election of November 2016,” The United States Census Bureau, April 2, 2019, <https://www.census.gov/data/tables/time-series/demo/voting-and-registration/p20-580.html>
- Holbein, John D. and D. Sunshine Hillygus, *Making Young Voters: Converting Civic Attitudes into Civic Action* (New York: Cambridge University Press, 2020).
- “Why Youth Don’t Vote: Differences by Race and Education,” CIRCLE at Tufts, August 21, 2018.
- Gray, Kathleen, “College Students Aren’t on Campus. Their Missing Votes Could Make Difference,” *New York Times*, October 20, 2020.
- Gurley, Gabrielle, “What Happens When You Can’t Catch a Ride to the Polls?: Voter-Suppression Tactics Can Create Transportation Challenges, Especially for Young People and Minorities,” *The American Prospect*, October 15, 2018
- Douglass, Raven, “Why We’re Fighting to Keep Polling Places on College Campuses,” <https://www.newsgroove.co.uk/why-were-fighting-to-keep-polling-places-on-college-campuses/>, February 17, 2020; Ellen Rolfes, “Why on-Campus Polling Locations Matter for College Students,” *Newsy*, October 22, 2020.

Cobler, Paul, “Democrats Challenge New Texas Limits on Polling Sites, Claiming It's GOP Response to Youth Surge in 2018,” *Dallas News*, November 1, 2019,

“State Laws on Voting Rights/Time Off to Vote,” *Workplace Fairness*, August 21, 2021, <https://www.workplacefairness.org/voting-rights-time-off-work>.

Harder, Joshua and Jon A. Krosnick, “Why Do People Vote? A Psychological Analysis of the Causes of Voter Turnout,” *Journal of Social Issues* 64, No. 3 (2008): 525-549.

Plutzer, Eric, “Becoming a Habitual Voter: Inertia, Resources, and Growth in Young Adulthood,” *American Political Science Association*, March (2002): 41–56

Morris, Kevin and Peter Dunphy, “AVR Impact on State Voter Registration: New Brennan Center Report Finds Significant Gains in Voter Rolls,” *Brennan Center for Justice*, April 11, 2019.

NCSL, “Automatic Voter Registration,” February 8, 2021, <https://www.ncsl.org/research/elections-and-campaigns/automatic-voter-registration.aspx>.

Niesse, Mark, “Almost All Eligible Georgians Are Registered to Vote, Data Show,” *The Atlanta Journal-Constitution*, August 19, 2021, <https://www.ajc.com/politics/almost-all-eligible-georgians-are-registered-to-vote-data-show/WVN373LTIZAN7IJECDODHRJWLM/>.

Velasquez, Angelina , “‘GOP Is About to Be Sorry’: Stacey Abrams Praised for Boosting Georgia’s Voter Registration to 95 Percent, Among Highest In the Nation,” *Atlanta Black Star*, August 22, 2021, <https://atlantablackstar.com/2021/08/22/gop-is-about-to-be-sorry-stacey-abrams-praised-for-boosting-georgias-voter-registration-to-95-percent-among-highest-in-the-nation/>.

Creek, Heather and Kyle Ueyama, “Why Are Millions of Citizens Not Registered to Vote?: A survey of the civically unengaged finds they lack interest, but outreach opportunities exist,” *The Pew Charitable Trust*, June 21, 2017, https://www.pewtrusts.org/-/media/assets/2017/06/ei_why_are_millions_of_citizens_not_registered_to_vote.pdf:

Holbein, John and D. Sunshine Hillygus, “Making Young Voters: The Impact of Preregistration on Youth Turnout,” *American Journal of Political Science*, Vol. 60, No. 2 (April 2016): 364–382

Gross, Andrew, "Number of Licensed Teen Drivers on the Rise," *AAA Newsroom*, November 19, 2020, <https://newsroom.aaa.com/2019/10/number-of-licensed-teen-drivers-on-the-rise/>.

"Family Educational Rights and Privacy Act (Ferpa)." *Home*, US Department of Education (ED), 25 Aug. 2021, www2.ed.gov/ferpa.

Bearer-Friend, Jeremy and Vanessa Williamson, "The I.R.S. Can Register Voters as Well as the D.M.V., and Maybe Better," *New York Times*, September 29, 2021

Reuter, Dominick, "1 Out of Every 153 American Workers Is an Amazon Employee," *Business Insider*, July 30, 2021

Huddleston, Justina, "Things You Don't Know about Fast Food Employees," *Mashed.com*, May 19, 2021, <https://www.mashed.com/124676/things-dont-know-fast-food-employees/>.

**Justice in Fyodor Dostoevsky's *The Brothers Karamazov*:
The Selfish vs. The Religious By Rosalinda Zhao**

Abstract

Two theories of justice are brought up by Zosima and his mysterious visitor in Fyodor Dostoevsky's *The Brothers Karamazov*. Fyodor Dostoevsky uses Mitya to demonstrate the reality of carrying out a worldly justice where justice for the individual is the sole concern of the individual. The reckless and abrasive Karamazov character is excused under this justice as many of Mitya's actions, though violent, serve the purpose of avenging his personal justice and getting back what is due to him. Justinian law qualifies Mitya's selfishness as justice with Dostoevsky's depiction of its three aspects of individual claim, obligation, and consistency within judicial application. Mitya also personifies one of Norman Care's theories of individual obligation in society for others--separate-life individualism. While Mitya's selfish justice believes in securing individual advancement through watching out only for oneself, the theory of justice Zosima and Christianity subscribe to typifies shared-life individualism--Care's theory that people with an understanding of the need to achieve justice for every individual will unite and work towards achieving that fate of satisfaction together because they believe everyone to be in the same boat. Zosima's advocacy for Christian brotherhood exemplifies this method of achieving justice for every society member's needs. This paper aims to justify Mitya's violent Karamazov actions and to explain the psychological motivation for one to follow Zosima's theory of selfless justice.

The Worldly Justice and Justinian Law

The vernacular language often makes no distinction between justice and righteousness. One of the clearest definitions that has been given historically is from the *Institutes of Justinian*. This sixth-century codification of Roman law calls justice "the constant and perpetual will to render to each his due" (Miller). In *The Brothers Karamazov*, Zosima's mysterious visitor explains the world as a place where "[everyone] will think his share too small and they will always envy, complain, and attack one another" (Dostoevsky 262), where justice is defined in the "freedom" to "have desires" and "satisfy them" for "you have the same rights as the most rich and powerful." Zosima expands on this idea, calling this worldly justice the "modern doctrine of the world...freedom" (Dostoevsky 270).

Mitya is one such man “accustomed to rely upon himself alone and to cut himself off from the whole; he has trained himself not to believe in the help of others, in men and in humanity, and only trembles for fear he should lose his money and the privileges that he has won for himself” (Dostoevsky 262). Though harshly worded, Zosima’s mysterious visitor describes a justice that believes in selfishness as the utmost virtue. Through various events in the novel, Dostoevsky builds Mitya as a character who aligns with Zosima’s mysterious visitor’s theory of the world’s selfish justice. Regardless of consequences for others, the world advocates for a justice of making sure one guarantees one’s own needs. By not believing in working for the common good, not believing in “the help of others,” Mitya makes decisions solely for himself such as going as far as threatening murder to get the money due to him and deciding to commit suicide if any aspect of his personal satisfaction cannot be met. He lives in the fear of “[losing] his...privileges” of seeking out personal gain in all of his ventures to such an extreme that he can be consumed within it enough to decide to take his life. Mitya, in following that modern doctrine and prioritizing the self over everything, epitomizes all aspects of the Justinian definition of justice--in individual claim, in obligation, and in consistency of justice--with his enactment of the worldly justice of entitlement.

Individual Claim Brings Justice

The role of freedom in this equation of worldly justice brought up by Zosima satisfies the aspect of Justinian justice for individual claim. Justice becomes a value in situations of competing claims, including claims to freedom. Philosopher David Hume points out the necessity of conflict for justice to be wrought since if “every individual finds himself fully provided with whatever his most voracious appetites can want...the cautious, jealous virtue of justice would never once have been dreamed of” (Hume 183-184). In regard to men’s desires in Zosima’s description of the world’s advancement in the pursuit of greed, men are told “Don’t be afraid of satisfying them and even multiplying your desires” (Dostoevsky 270). Inevitably, there will come a clash of wants and needs between men in the world with this guiding principle of freedom in their actions. Justice will be implemented to resolve conflict by defining entitlement. Entitlement is central to this aspect of Justinian justice. Giving “to *each* his due” revolves around what an individual wants, not what would create the most good for an entire society. An individual with only his self’s gain prioritized will have clearcut wants. Without such a stark

cutout of individual desires, justice would not be the prominent value carried out. For example, if individual gain is not the priority, other values like charity and making sure everyone gets a share will overrule any just decision. If Mitya cared about his father receiving enough to comfortably live through old age, it would be understandable if he decided to let his father keep more than his share of the property split between them. However, this would not be an act of justice, because the just decision would be to evenly split their assets. Filial piety would overrule justice.

Therefore, Dostoevsky's depiction of Mitya encapsulates the individual claim in Justinian justice. Justice becomes the biggest value in evaluating the right step to go forward in Mitya's decision-making because Mitya clears away all those other values like sharing and focuses solely on the advancement of the self, like the doctrine of the world tells him to. He demands money violently from his father because what his "due" in Justinian law is the money owed to him and principles like empathy and sensitivity do not unite his interests enough with another person for him to choose compassion or to decide to just forgive the debt. Justice is only served if he gets his due and because of his focus on entitlement, the pursuit of this justice will not be overthrown by the value of acting in the common good.

Mitya exemplifies this worldly sense of justice to an extreme before his trial. All his Karamazov-typical actions are justified under the right of self-entitlement. These actions may not typically fall under the Christian sense of righteousness, but one can acknowledge the consistent devotion to Justinian law in Mitya's hunt for justice. Known for getting into brawls at bars, Mitya lives a life peppered with examples of violent actions that would not be ethically excusable under Christian standards, but would be considered warranted under this self-serving justice. The many public demonstrations Mitya puts on, threatening his father with even murder if he does not give him money, populate the novel. When Mitya was younger, he would also be quick to fight duels while serving in the military. Christian messages of forgiveness and peacefulness unquestionably do not condone these actions, but within the pursuit of his self-interest, Mitya is justified. Duels were methods of fair repercussions, to sort out right and wrong, provide revenge for the wronged. The townsman narrator reveals later in the novel that Mitya's father may have really owed Mitya money and refused to give it up, out of the stubbornness of his character. Mitya's recklessly aggressive manner towards his father is excused under the circumstances that he is only defending his own case, trying to get back the money he is entitled to.

The Obligation of Justice

Not only is Mitya's violence in such cases condoned by the *Institutes of Justinian's* definition of justice, but it would also be an act of injustice for Mitya to *not* carry out this violence. After all, justice is a "due" that must be paid. Justice in the Justinian definition is distinct from other virtues because unlike other virtues, mankind expects justice in every situation. No other virtues are held to this standard of consistency. People do not mind if one does not exude kindness or participate in philanthropy in every act, but they will be quick to raise their fists in protest if they do not believe justice has been properly served. Due to the property of justice always being *due* to someone, justice can be likened to a contract. Because "we demand justice, but we beg for charity or forgiveness," justice has a component of obligation other virtues do not (Miller).

There exists an agent that the obligation falls on. If the agent does not carry out justice, the wrong falls now on the agent too, putting him also in a coop of wrong with the wrongdoer. The father's misdeed in not giving Mitya the money he should be receiving gives Mitya the obligation of an agent of justice. Mitya knows his father did not distribute the money properly to him; the responsibility to make sure his father corrects that wrong now falls on Mitya. Regardless of whether his means of correcting that wrong manage to demonstrate other virtues like compassion or other traits of good character, Mitya has acted against injustice and acted on the obligation of bringing justice.

Mitya's Selfish Justice

Thinking he no longer had any romantic chance with Grushenka, Mitya decides to commit suicide after the incident with Grigory, not because he wanted to leave the happy couple alone as he claims to, but because of the sole reason he no longer sees his personal fulfillment possible in a relationship with Grushenka if she has chosen her former love. He carries out the worship of pursuing his own desire to the utmost by choosing suicide when any obstacle comes in the way of his self-fulfillment. Mitya outlines his thought process for the hopelessness of his situation in the love triangle of Grushenka, her first love, and him: "Here there was no room for dispute; it was her right and his; this was her first love which, after five years, she had not forgotten; so she had loved him only for those five years, and I, how do I come in? What right

have I? Step aside, Mitya, and make way! What am I now?" (Dostoevsky 350). The "his" Mitya refers to in "her right and his" is the right of Grushenka and her first love. Under the worldly justice, they have the right to pursue this romance, notwithstanding Grushenka's previous relationship with Mitya, because they have the right to pursue what is in their best interest--for both, it would be to rekindle their former relationship. The "right" Mitya asks of himself in the question "What right have I?" refers to the same right.

Mitya's lack of right does not come from a place of discomfort of being placed into a potential love triangle. If he thought he was imposing in a love triangle, he would have been uncomfortable long ago, as he was already in one with Grushenka and his own father beforehand. He did not have any motivation for suicide then because he did not see his father as a total threat and believed in his own chances for getting Grushenka to return his love. The change now is that he believes Grushenka, given the option of her first love, will never choose him. He does not see where he "[comes] in" or where his right is because if, as he assumes then without a doubt, Grushenka has chosen her first love, any continual suitor's pursuit would be fruitless for him without the possibility of any return of his love. The relationship would be one-sided and Mitya would not benefit from it. Without being able to receive anything, Mitya is treated unjustly under the terms of the world's protection of self-interest.

Mitya achieves the ultimate extreme of the world's individualism when he decides to commit suicide exclusively because of this lack of any returned love in his relationship with Grushenka. Any aspect of his life that cannot bring personal gain is unbearable for him and even a detail of his love life is a heavy enough straw to break his will to live. Mitya is a fulfillment of what Zosima's mysterious visitor predicted--that any man of the world who was not able to receive gain from everything they did would "even commit suicide if they are unable to satisfy it" (Dostoevsky 270). Later on, during trial interrogations, Mitya's quick response to questions of why he planned to commit suicide demonstrates how streamlined the decision was for him since he only evaluated personal gain as a value. When probed by the prosecution about the planned suicide, Mitya's answers with an uncomplicated motive: "Well, I made up my mind to kill myself. What had I left to live for? That question stared me in the face. Her first rightful lover had come back, the man who wronged her but who'd hurried back to offer his love, after five years and atone for the wrong with marriage.... So I knew it was all over for me" (Dostoevsky 405). Mitya was able to "[answer] briefly and abruptly" because he reduced the decision to either

live a life lacking in the pursuit of his own gain or take the worldly freedom of making the choice of suicide. In his reasoning, he might as well commit suicide because he cannot achieve what he wants in his self-interest. This injustice seems fatal to Mitya.

The Hypocrisy in Justice without Consistency

For a theory of justice to be considered followed, there must be consistency in how the justice is applied to situations. The Justinian application of justice requires the “constant and perpetual will.” The language Mitya uses in his suicidal reasoning, telling himself to “Step aside, Mitya, and make way!” may appear to be an enlightened moment of selflessness in Mitya’s life, but his aspirations are unfortunately hypocritical. He paints a picture of himself following a righteous justice where he gives up his personal interest in a relationship with Grushenka for the happiness of the couple, but since there is no consistency in following the rules of this selfless justice, this philosophy does not stand as a valid justice. Mitya’s nature subscribes to a philosophy that makes him a man who carries out the world’s justice by only looking out for himself. The wording of his reasoning to “make way” may give it the shine of Christian selflessness, but a closer examination of the situation establishes the untruth in his words. Mitya uses an analogy of a driver, frantically addressing a driver he seizes by the shoulders, “Then you know that one has to make way. What would you say to a driver who wouldn’t make way for anyone, but would just drive on and crush people? No, a driver mustn’t run over people. One can’t run over a man. One can’t spoil people’s lives. And if you have spoiled a life--punish yourself.... If you’ve spoiled a life, if only you’ve ruined any one’s life--punish yourself and go away” (Dostoevsky 351). If one had no knowledge of any part of Mitya’s life, Mitya’s frenzied sermon might seem like a noble principle for Mitya to believe in. However, any degree of remote familiarity with Mitya’s character demonstrates that Mitya preaches selflessness in name only, and has never practiced such virtuous actions in reality.

His conduct is full of not “[making] way for anyone,” continuing to “just drive on and crush people.” The townsman narrator gives a prominent example, typical of Mitya’s daily behavior, where Mitya completely humiliates a captain and his son when he drags the captain by the beard down a street. In fact, the cruel action causes irreparable damage to the captain’s son’s psyche, as Ilyusha struggles for the rest of the book to come to terms with the insult to his father’s honor. Not only does Mitya constantly walk around town threatening people, even his

own father, he feels no shame or fear in doing it openly. It seems all Mitya does is “run over people.” Until his decision to commit suicide now, he has never displayed any guilt or desire to inflict punishment on himself over the many lives his infamous Karamazov disposition has spoiled. Yet in this lecture, Mitya is adamant that if a man should ruin even one life, he must take it upon himself to “punish [himself] and go away.” For Mitya to publicly humiliate the captain and his son or for Mitya to continue to impose himself in a love triangle to break apart a happy relationship would both be situations where he would be spoiling lives. Despite the similar consequence of spoiled lives, Mitya chooses to feel no guilt or have any afterthoughts about the captain while he claims his sin in the situation with Grushenka and claims to be even willing to inflict punishment on himself, something that seems to run most contrary to his selfish philosophy. The difference between the two unpleasant situations, the real reason for Mitya’s differing actions, is that with the captain’s shaming, he suffers no loss in terms of his own interest, whereas Grushenka’s case now works against his egocentric motivation. Mitya’s true motivation for “making way” remains self-serving.

The justice Mitya claims to be following in giving the couple space does not hold up as a philosophy of justice because of its lack of consistency. Mitya has decided when and where he wants to claim to be following it when, for the most part, he has lived blatantly in opposition to it. The case of love triangles with his father or with Grushenka’s former love are relevantly similar for the purposes of Mitya reasoning to back out by suicide. For a constant application of rules, all similar cases would have to have the same result of justice dispensed. Mitya has also shown himself not to be impartial in the dispensation of the justice he describes. His judicial feelings towards his father do not match his feelings towards Grushenka’s former love. For the justice of making way to be a valid Justinian justice, there would need to be consistency and impartiality in its application. By contrast, Mitya’s selfish justice is further validated because there is commonality in his actions with Grushenka and his aggressive threats. He always progresses in the field of greed, and when he sees no more advancement, he retreats.

The only justice described in *The Brothers Karamazov* that typifies Justinian justice in all its aspects is Mitya’s selfish justice. The focus on the self determines what is “due,” allowing individuals to claim their personal dues. Conflicts between individual interests encourage the involvement of justice rather than charity to settle them. The entitlement attached to individual interest is captured in the “rights” the world tells men they have regardless of if it is towards their

property, their interpersonal relationships, or their pursuit of personal gain. The selfish justice also qualifies the Justinian requirement of obligation as Mitya regularly confronts individuals who do not give him the proper amount of money he is due. As the agent responsible with obligation, Mitya makes haste in guaranteeing the proper allotment of his dues, and it doubly aligns with his goal in seeking personal benefit because he receives more money. Lastly, Mitya is consistent and impartial in deciding to go ahead with the act that will guarantee his own dues. He chooses to remain in the love triangle with his father because he knows to drop out would ruin his chances with Grushenka and work opposite to what he wanted--Grushenka's love. He chooses to commit suicide once he believes Grushenka has chosen her former love because he knows even if he continued his pursuit of his love interest for the next ten years, it would be in vain because she would not return his love and he would end up suffering. Such a result would not be ideal if he is one that looks out for himself. The selfish, obligatory, and consistent application of the worldly justice Zosima's mysterious visitor introduces proves itself to be a piece of law belonging to the Justinian code and Mitya's actions are justified under it.

Zosima's Christian Brotherhood as Shared-Fate Individualism

The worldly justice is described by Zosima's mysterious visitor with such scorn because he contrasts this sort of individualism with the social security and brotherhood of Christian justice. He pits the Roman law's description of justice against the unification Christian justice would bring. The visitor separates Christianity from worldly notions of justice because "[no] sort of scientific teaching, no kind of common interest, will ever teach men to share property and privileges with equal consideration for all" like a Christian "brotherhood" (Dostoevsky 261). Though Zosima as a monk may appear to be biased in his motivation for depicting Christianity as the right route of justice, his theories of worldly justice remain credible as he correctly predicts the negative consequences of the worldly justice on Mitya. Zosima boldly claims that "men [will] even commit suicide if they are unable to satisfy [their desires]" (Dostoevsky 270). Zosima details a justice, drastically different from the worldly justice, where men learn to put aside their personal gain, since "true security is to be found in social solidarity rather than isolated individual effort" (Dostoevsky 262). He dreams of a world where even servants are offered to have tea once in a while because it seems unjust for a sinful man to be worthy of servantry. He questions why a servant might serve a sinful man, who himself might be deserving

of entering servantry. Zosima bases determination of injustice on empathy, looking at the servant's view of serving the master instead of the master's entitlement.

In *On Sharing Fate*, Norman S. Care lays out two sorts of obligation justice sets on a person. The first sort, self-responsibility, is the fulfillment of individual potential familiar to Mitya. The second sort, other-responsibility, is what Zosima believes the world will be converted to. Other-responsibility requires consideration of others and for the individual to be accommodating of what will help others fulfill their potential. The brotherhood and "grand and simple-hearted unity" (Dostoevsky 272) Zosima describes is what Care calls one of the two attitudes "similarly deep and equally fixed" in usual definitions of morality. People commonly hold the ethical attitude that each member of society is "in life together" and that there is a shared moral background. The shared moral beliefs are so strong that Care argues "fate is shared" within such a moral community. The second commonly-held attitude is part of the foundation of Mitya's justice: people are autonomous, separate beings with "but one life to lead" (Care 35). Mitya, along with the other men of the world, have great freedom in excusing their actions under the worldly justice because they can lay claim to the fact that they only have one life to pursue what they want. Care argues that all men share these two common attitudes, but the main issue men differ on in philosophies of justice is "the moral standing of one's own life, relative to the lives of others, in different circumstances" (Care 36). In other words, different notions of justice, such as the justices of Christianity against the world, differ on the consideration an individual should give towards others.

The two ends of the spectrum of balancing consideration for others with personal needs can be outlined with separate-life individualism and shared-fate individualism. The "terrible individualism" Zosima describes to be the worldly justice is, in Care's terms, separate-life individualism. Separate-life individualism focuses on the second attitude, on the separation of individuals, into "units" and individual "grooves" as Zosima calls them (Dostoevsky 262). American philosopher Robert Nozick defends this "radical individualism" as the "fact of our existences" (Nozick 33). Under separate-life individualism, Mitya can be "immune to moral challenges based on comparison with the frustrated lives of others" (Jenni 797-798). Mitya can drag the captain by the beard down the street, demanding for his money, regardless of the frustration the captain and his son will suffer from the captain's insulted honor and public humiliation. Nozick further absolves blame or crime in Mitya's Justinian actions since this

individuality “characterizes us from birth to death, is wholly independent of our volition, and is susceptible of qualification normatively or with respect to degree” (Norton 113). In other words, Nozick makes a case for nature being the root cause for selfishness rather than nurture or a nurtured tendency for evil and selfishness.

On the other hand, Care is more inclined to agree with Zosima’s condemnation of separate-life individualism rather than use it to justify Mitya’s actions. Care’s book *On Sharing Fate* concludes with his stance that separate-life individualism--an “alternative to shared-fate individualism”--does not “[give] sufficient moral guidance for the resolution of contemporary human problems” (Mulvaney 81). Shared-fate individualism prioritizes the first commonly-held attitude of being “in life together.” Zosima believes in brotherhood, but his brotherhood does not oppose the interest of obtaining individual satisfaction. Zosima does not advocate for the sacrifice of every individual’s happiness when he preaches to give up worldly desires. Brotherhood is merely a different method of obtaining individual gain. In shared-fate individualism, individuals are willing to go into service for others rather than for themselves because the society is just only when every member achieves self-realization. Mitya’s method guarantees justice for the individual; shared-fate individualism aims to guarantee justice for every individual by creating a common moral community.

Care recommends that individuals can work towards achieving individual self-realization for an entire community through service careers (Care 40). Zosima’s vision of the religiously just future shares the belief in service for the common good. Zosima does not explain brotherhood as being reached through the mere alignment of purposes in a community. He specifically states that to fight for the cause of humanity, individuals must “[serve] the cause of brotherly love and the union of humanity” (Dostoevsky 270). He emphasizes service as what will bring all these isolated worldly individuals back into concern with the rest of humanity. He tasks the future generation with the clear message: “You are working for the whole” (Dostoevsky 278). The “whole” is the moral community Care discusses. Other Christian values Zosima brings up in his discussion of this shared-fate individualism only add to the central vision of this moral community. When Zosima talks about the balance between members of his ideal society such as when the rich will be “ashamed of his riches before the poor” and the poor will understand this humility and react “joyfully and kindly to his honorably shame,” each member of this situation, both the poor and the rich, are sacrificing personal greed or gloating to help each other achieve

self-realization. Because both sides are interested in helping the other side live the happier life they justly deserve, they will give into the “equality...to be found only in the spiritual dignity of man.” The common agreement Care talks about in a moral community is what Zosima says “will only be understood among us” and is present in that push-and-pull example between the rich and the poor (Dostoevsky 272). Zosima’s justice for all individuals reached through social solidarity and a common fraternity is a representation of Care’s shared-fate individualism, whereas Mitya’s selfishness represents separate-life individualism.

These different notions of justice present alternative practices of achieving justice through fulfilling individual needs. However, though Mitya decides to commit suicide out of the lack of personal gain in his relationship with Grushenka, he never actually follows through with it. Zosima preaches extensively on the proper conduct of men and monks in the world, but still leaves behind the stinking body of an unsaintly man. In typical Dostoevsky fashion, Fyodor Dostoevsky has given an inconclusive discussion of two opposing theories of justice.

References

- Care, Norman S. *On Sharing Fate*. Temple University Press, 1987.
- Dostoevsky, Fyodor. *The Brothers Karamazov*. Translated by Susan McReynolds, 2nd ed., W.W. Norton & Co., 2011.
- Hume, David. *Enquiries Concerning Human Understanding and Concerning the Principles of Morals*. Clarendon Press, 1975.
- Jenni, Kathie. "On Sharing Fate." *Noûs*, vol. 24, no. 5, 1990, pp. 797-803.
- Miller, David. "Justice." *Stanford Encyclopedia of Philosophy*, 2021, edited by Edward N. Zalta, <https://plato.stanford.edu/entries/justice/>. Accessed 25 August 2021.
- Mulvaney, Robert J. "Review: What Morality Requires." *Behavior and Philosophy*, vol. 18, no. 1, 1990, pp. 81-83.
- Norton, David L. "Individualism and Productive Justice." *Ethics*, vol. 87, no. 2, 1977, pp. 113-125.
- Nozick, Robert. *Anarchy, State, and Utopia*. Basic Books, 1974.

A Snapshot of Several Major Cytokines in Multiple Sclerosis by Rishi Gadikota

Background

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease affecting approximately 400,000 people in the United States and 2.1 million people worldwide.(Dilokthornsakul et al.) Its consequences can range from mild symptoms to degradation of the quality of life, relationships, employment, and productivity.(Phillips; Rao et al.) With an estimated lifetime cost per MS patient of over \$4 million, MS is the second-ranked chronic condition (behind congestive heart failure) in direct all-cause medical costs.(*Six Cost Drivers of Multiple Sclerosis*) For the U.S., the total estimated cost of MS is \$28 billion per year.(*Six Cost Drivers of Multiple Sclerosis*)

MS is a neurodegenerative, demyelinating disease targeting the oligodendrocytes of the central nervous system. MS presents itself majoritively in women, especially young women. It is more prevalent in higher latitudes.(“Causes and Risk Factors of Multiple Sclerosis”)

The exact cause of MS is unknown but believed to be a combination of a genetic predisposition and environmental exposure. MS is an autoimmune disorder targeting the body’s myelin. MS causes blood-brain barrier (BBB) damage, which allows for immune cells of the body, such as macrophages and lymphocytes, to break through the BBB, and enter the CNS, where they can then attack the oligodendrocyte myelin. As these cells attack and degrade the myelin, the nerves the myelin is insulating become inflamed or damaged. When seen on imaging, these areas of inflammation are known as lesions or plaques.(“The Immune System and Multiple Sclerosis”)

MS is characterized by symptoms spread across time and space, where patients would not come in repeatedly with the same symptoms, but often with different symptoms each time and over varying time intervals. Despite this unpredictability, several symptoms do commonly occur ([Table 1](#)).

Fatigue	Speech disorders
Walking (gait), balance, and coordination problems	Swallowing problems
Bowel dysfunction	Headache
Dizziness and vertigo	Hearing loss
Pain	Seizures
Emotional changes	Tremor
Spasticity	Respiration/breathing problems
Numbness	Itching
Bladder dysfunction	
Vision problems	
Sexual dysfunction	
Cognitive dysfunction	
Depression	

The most commonly affected areas are the optic nerve, deep cerebral white matter, the brainstem, and the spinal cord. This explains many of the common symptoms (ex., vision problems due to demyelination of the optic nerve) and the inconsistency of these symptoms.

Currently, four basic disease courses have been identified for MS. These are clinically isolated syndrome, relapsing-remitting, secondary progressive, and primary progressive multiple sclerosis.

MS itself is rarely fatal, but complications from MS, such as swallowing difficulties, bladder infections, etc., often occur and are often the ultimate cause of death. Many treatments have been developed to make the lifestyle of those with MS more bearable. The average lifespan of those with MS is around 5-10 years lower than that of the average person, but this gap slowly diminishes with developing therapies. (“Multiple Sclerosis”)

This report will discuss the role of major cytokines involved in multiple sclerosis and their potential as MS therapies.

Currently, there is no cure for multiple sclerosis. However, several therapies focus on speeding recovery from relapses, slowing the progression of MS, and managing associated symptoms. Treatments for recovery from MS attacks include corticosteroids and plasma exchange. A remedy for slowing the progression of MS includes ocrelizumab. Note that there are many other treatments, depending on the variation of illness and an individual’s conditions. New therapies currently underway focus on several aspects of MS, namely, stopping MS in patients, restoring damaged myelin, and ending MS for future generations.

The Role of the Interleukin-13 Receptor in Multiple Sclerosis

Background

The interleukin-13 receptor is a type I cytokine receptor. Interleukin-13 and Interleukin-4, often studied in tandem, can downregulate the synthesis of T-helper type 1 proinflammatory cytokines, and thus, are considered anti-inflammatory cytokines. (*Neuroimmunology of the Interleukins 13 and 4*) As their role in the brain is further investigated, it has been suggested that these molecules have a possible role in neurodegeneration. This portion will discuss the major literature regarding the potential role of the interleukin-13 receptor in multiple sclerosis.

Effects and Therapeutic Potential in Multiple Sclerosis

IL-13 has been suggested to have a neuroprotective role in MS and may have a role in future therapies. (*Neuroimmunology of the Interleukins 13 and 4*) IL-13 and IL-4 are considered anti-inflammatory due to their ability to downregulate the production of pro-inflammatory cytokines. Due to this, studies have now looked to IL-13 as a potential target to ease inflammation in MS. A study using immune cells from both MS patients and healthy donors utilized a synthetic, IL-13 treated monolayer (to represent the blood-brain barrier) composed of a layer of human brain endothelial cells and meningeal endothelial cells, both collected from a healthy brain. (Hoornaert) Adding IL-13 to the model significantly raised the production of vascular cell adhesion molecule-1 (VCAM-1) — a molecule that promotes the binding of certain types of immune cells to blood vessels. (Hoornaert) This cytokine also enhanced the barrier properties of human brain endothelial cells and meningeal endothelial cells, as evidenced by increased tight junction components — specialized connections between cells that act as ‘molecular gates’ to regulate the diffusion of molecules. This enhancement ultimately increased the tightness and integrity of the blood-brain barrier, therefore reducing its permeability. (Hoornaert) By boosting the BBB’s barrier properties, infiltration from the bloodstream’s immune cells will decrease. This may allow for damaging inflammation to be reduced. Another study examined cytokines and other inflammatory markers in a large group of patients with MS. It established the anti-inflammatory cytokine IL-13 as having a significantly higher concentration in the MS group than the control group. (Martins et al.) IL-13 concentration also differs within patients of the same variation of MS, with one study establishing higher percentages of CD4+ helper T cells producing IL-13 amongst patients in relapse versus patients

in remission.(Ghezzi et al.) During a relapse, IL-13 would play a role in anti-inflammatory processes to prevent excess inflammation while new symptoms emerge.

On the other hand, IL-13 would no longer need to act nearly as strongly during remission, as inflammation is not as prevalent in that scenario. This supports the potential of IL-13 as an actor in inflammation reduction. The prevalence of IL-13 in multiple sclerosis, however, remains controversial. There remains a variety of studies investigating the role of IL-13 in MS, and therapies relating to IL-13 remain under discussion. Further supporting this potential is IL-13's role in glatiramer acetate (GA) treatment. GA is effective in the treatment of MS through stimulation of myelin and blockage of myelin-damaging T-cells. This blocking mechanism is not fully understood, but one study has demonstrated that IL-13 is necessary for this mechanism.(WIESEMANN et al.)

Conclusion

Appropriate therapies could concentrate on the potential neuroprotective role of IL-13, as it could be influential in its anti-inflammatory properties. Such therapies may reduce damaging complications of MS

The Role of CXCL12 in Multiple Sclerosis

Background

CXCL12 is a chemokine member of the intracrine family. It plays a role in many diverse cellular functions, such as being the ligand for the G-protein coupled receptor, embryogenesis, immune surveillance, inflammatory response, tissue homeostasis, tumor growth, and metastasis. A disease associated with CXCL12 includes Whim Syndrome, which is caused by a mutation of CXCR 4 (CXCR 4 is the receptor for CXCL12).(CXCL12 Gene - GeneCards | SDF1 Protein | SDF1 Antibody) This portion will discuss the significant literature regarding the potential role of CXCL12 in multiple sclerosis.

Effects and Therapeutic Potential in Multiple Sclerosis

In healthy physiology, CXCL12 is a chemokine that is expressed constantly by the CNS. This points to a potential role in maintaining the blood-brain barrier.(CXCL12 Limits Inflammation by Localizing Mononuclear Infiltrates to the Perivascular Space during

Experimental Autoimmune Encephalomyelitis | The Journal of Immunology) It is detected on the outer surface of the CNS endothelium and functions to restrict the entry of infiltrating leukocytes. However, in individuals with CNS autoimmune diseases, such as MS, this expression is altered, and the chemokine moves to the inner side of the microvasculature. This prompts enhanced activation of CXCR4 on infiltrating leukocytes. This may prompt improper leukocyte movement through the BBB, and consequently, contribute to the severity of MS.(McCandless et al.) One study focused on the non-inflammatory role of CXCL12, using the mouse model of experimental autoimmune encephalomyelitis (EAE) to represent multiple sclerosis. CXCL12 was found to prevent CXCR4-expressing mononuclear cells from infiltrating the CNS parenchyma, where the cells would contribute to microglial activation and demyelination.(*CXCL12 Limits Inflammation by Localizing Mononuclear Infiltrates to the Perivascular Space during Experimental Autoimmune Encephalomyelitis | The Journal of Immunology*) This points against CXCL12 functioning as an inflammatory cytokine. Other studies support this as well, suggesting that CXCL12 normally functions to localize leukocytes to perivascular spaces, while altered expression of CXCL12 may not allow such relocation, and thus, leads to BBB infiltration and the further progression of MS.(*Pathological Expression of CXCL12 at the Blood-Brain Barrier Correlates with Severity of Multiple Sclerosis - PubMed*)

CXCL12 has been determined to have potential as a therapeutic, though there remain highly contradictory results. This is evidenced by a study in which the potential of NSC-87877, a treatment that increases the expression of CXCR7, was evaluated in the treatment of EAE. This treatment induced the expression of CXCR7, which resulted in reduced T-cell trafficking in response to CXCL12.(Luo et al.) Furthermore, it has also been shown that CXCL12 inhibits the movement of infiltrating cells from the perivascular space into the brain parenchyma, thereby limiting inflammation. However, a different study has reported a loss of CXCL12 from the outer surfaces of the blood-brain barrier in MS lesions, and therefore, a treatment that prevented CXCR7 from sequestering CXCL12 resulted in elevated CXCL12 in these outer surfaces and reduced leukocyte infiltration, which dampens the severity of EAE.(Dhaiban et al.)

Conclusion

Relevant therapies could concentrate on the anti-inflammatory role of CXCL12 in its inhibition of cellular infiltration of the brain parenchyma. These anti-inflammatory properties

may play a vital role in future MS treatment, especially when considering the damaging complications resulting from excess inflammation due to MS. Research remains highly controversial, with both pro-inflammatory and anti-inflammatory roles having been identified depending on the context. Future research may concentrate on elucidating the molecular underpinnings that influence the pro or anti-inflammatory behavior of CXCL12.

The Role of GM-CSF in Multiple Sclerosis

Background

Granulocyte-macrophage colony-stimulating factor (GM-CSF) was initially described as a growth factor that promotes the differentiation of myeloid progenitors in the bone marrow.(Lotfi et al.) GM-CSF has an important cytokine effect in chronic inflammatory diseases by the stimulation, activation, and migration of myeloid cells to certain sites of inflammation. This promotes the survival of target cells and stimulates the renewal of effector granulocytes and macrophages. Therefore, an imbalance in GM-CSF production or signaling may lead to harmful inflammatory conditions. In this context, GM-CSF has a pathogenic (contributing to disease progression) role in autoimmune diseases that are dependent on cellular immune responses such as multiple sclerosis (MS) and rheumatoid arthritis (RA).(Lotfi et al.) This portion will discuss the major literature regarding the potential role of GM-CSF in multiple sclerosis.

Effects and Therapeutic Potential in Multiple Sclerosis

A certain study using the animal model of MS, EAE, has shown that GM-CSF production by pro-inflammatory T cells, but not CNS resident or other peripheral cells, was required for EAE onset. Furthermore, data from the study has illustrated that GM-CSF is a critical cytokine required for the initial CNS inflammation associated with EAE, and likely plays a similar role in MS. GM-CSF may contribute to the progression of MS by boosting the production of inflammatory cytokines such as IL-1, IL-6, and TNF α , all of which further influence the ruination of the myelin sheath (the primary problem in MS).(GM-CSF Production by Autoreactive T Cells Is Required for the Activation of Microglial Cells and the Onset of Experimental Autoimmune Encephalomyelitis | *The Journal of Immunology*) Other studies have supported this function, namely with the unique relationship between IL-23 and GM-CSF production. IL-23 is required for GM-CSF production, through which it increases

pro-inflammatory myeloid cells in the CNS, resulting in demyelination in EAE. Combined with other evidence, it has been suggested that there may be a positive feedback loop between GM-CSF and IL-23.(Hartmann et al.) The function of GM-CSF has been clinically supported as well, with a study finding that MS patients have an increased number of GM-CSF-producing (GM-CSF+) CD4+ T cells in the blood. The researchers showed that GM-CSF+ CD4+ T cells are numerous in the lesions of untreated MS patients and that the number of these cells decreases after an anti-inflammatory IFN- β treatment. The group also observed that GM-CSF+ CD8+ cytotoxic T cells are present in MS lesions.(Hartmann et al.) This supports GM-CSF's pathogenic role in EAE and MS. These results strongly support the inhibition of GM-CSF as a therapeutic intervention in MS. Results from phase I studies indicate a favorable safety profile of antibodies against GM-CSF, therefore supporting it as a potential therapeutic strategy.(Aram et al.)

Conclusion

GM-CSF plays a significant pathogenic role in MS, mainly through inducing the increased production of inflammatory cytokines. Future studies may concentrate on its potential in relation to therapeutic strategies.

The Role of IFN- γ in Multiple Sclerosis

Background

IFN- γ was initially discovered as an antiviral agent, being a glycoprotein with a range of immune functions, including the promotion of macrophage activation, mediation of antiviral and antibacterial immunity, enhancing of antigen presentation, etc. This gene is mainly secreted by activated T-cells and natural killer (NK) cells.(Tau and Rothman)

Effects and Therapeutic Potential in Multiple Sclerosis

IFN- γ production had long been thought to be a trademark of T helper (Th)1 cells that cause inflammation and drive autoimmunity, such as MS.(Tau and Rothman) After this, IFN- γ had been observed to have a protective role by generating regulatory cell activity and modulating the effector T cell response.(Tau and Rothman) In EAE, some innate and adaptive immune cells exhibit opposing roles that are intimately linked to the generation of IFN- γ .(Tau and Rothman)

More recent data, however, support stage-specific IFN- γ involvement in EAE, offering a possible explanation of previously contradictory results. IFN- γ is a cytokine significantly detected in MS lesions, and its levels rise dramatically as the disease progresses. Inflammation is linked to an IFN- γ producing Th1 response in both MS and EAE.(Lees and Cross) However, it has been shown that a shift towards a Th2 producing response as opposed to a Th1 response may alleviate EAE in rodent MS models.

Recent research has demonstrated both advantageous and disadvantageous effects of IFN- γ . Trialed IFN- γ administration to patients with MS has been shown to worsen their clinical condition, resulting in a higher number of relapses in patients. In EAE and other demyelinating animal models, however, some investigators have demonstrated that IFN- γ may actually be advantageous.(Lees and Cross) Those rodents lacking IFN- γ or its receptor, as well as rodents administered anti-IFN- γ antibodies, all developed a much more severe condition than those rodents which possessed these aspects, suggesting that IFN- γ may actually play a role in limiting disease.(Lees and Cross) Furthermore, IFN- γ treatment of oligodendrocytes may make them less vulnerable to the oligodendrocyte toxin cuprizone, according to results from experiments using the toxin.(Lees and Cross) In a preliminary clinical trial, seven of eighteen RRMS patients treated with IFN- γ had symptom exacerbations, confirming the proinflammatory effects of the drug.(Arellano et al.) Consistently, secondary progressive MS patients (SPMS) treated with antibodies against IFN- γ exhibited slightly reduced clinical symptoms. Secondary progressive MS patients (SPMS) treated with anti-IFN- γ antibodies consistently showed a small reduction in clinical symptoms. Given this compilation of evidence, the conflicting actions of IFN- γ in MS and the many EAE models remain unresolved.(Arellano et al.) However, research suggests that these contradictory effects are due to IFN- γ 's differential temporal roles in EAE, which include increasing pathogenesis during the initiation phase but immunosuppression during the effector phase. During the initiation phase, an intrathecal IFN- γ expression system prompted an earlier disease start followed by recovery, whereas in the chronic phase, overexpression of IFN- γ resulted in disease amelioration.(Arellano et al.) Intraventricular injection of IFN- γ during the start phase consistently enhanced the number of relapses in chronic-relapsing EAE (CREAE) animals.(Arellano et al.) Given all of this recent evidence, the role of IFN- γ remains controversial, and much remains to be investigated.

Conclusion

While it is possible that IFN- γ treatment may play a key role in future MS therapies, much remains to be elucidated about the nuances and importance of timing in this role. Future research may concentrate on this timing and in what way that this timing affects the severity of RRMS.

Concluding Remarks

The implications of MS on one's lifestyle, health, and well-being are severe. Genetic therapies, such as those involving cytokines, may play a key role in future treatment and prevention of MS. With the increasing advancement of current biomedical technology, it may be possible to see a future in which the implications of MS could be greatly reduced. The cytokines CXCL12, GM-CSF, IFN- γ , and the IL-13 receptor are not alone, as there are many other cytokines with a large role in the pathogenesis of MS or great potential in its treatment.

Based on this analysis, future research on the contributions of cytokines to MS pathogenesis and potential treatments is critical, and appears to be a promising avenue to advance therapeutics for millions of affected patients.

References

- Aram, Jehan, et al. "Granulocyte-Macrophage Colony-Stimulating Factor as a Therapeutic Target in Multiple Sclerosis." *Neurology and Therapy*, vol. 8, no. 1, June 2019, pp. 45–57. *Springer Link*, <https://doi.org/10.1007/s40120-018-0120-1>.
- Arellano, Gabriel, et al. "Stage-Specific Role of Interferon-Gamma in Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis." *Frontiers in Immunology*, vol. 6, Sept. 2015, p. 492. *PubMed Central*, <https://doi.org/10.3389/fimmu.2015.00492>.
- Brainstem | Definition, Structure, & Function | Britannica*.
<https://www.britannica.com/science/brainstem>. Accessed 26 Sept. 2021.
- "Causes and Risk Factors of Multiple Sclerosis." *Verywell Health*,
<https://www.verywellhealth.com/multiple-sclerosis-causes-and-risk-factors-2440716>.
Accessed 21 Sept. 2021.
- Cellular Differentiation - an Overview | ScienceDirect Topics*.
<https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/cellular-differentiation>. Accessed 19 Sept. 2021.
- Chemokine - an Overview | ScienceDirect Topics*.
<https://www.sciencedirect.com/topics/medicine-and-dentistry/chemokine>. Accessed 19 Sept. 2021.
- Clinically Isolated Syndrome (CIS) | National Multiple Sclerosis Society*.
[https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Clinically-Isolated-Syndrome-\(CIS\)](https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Clinically-Isolated-Syndrome-(CIS)). Accessed 17 July 2021.
- CXCL12 Gene - GeneCards | SDF1 Protein | SDF1 Antibody*.
<https://www.genecards.org/cgi-bin/carddisp.pl?gene=CXCL12>. Accessed 25 July 2021.
- CXCL12 Limits Inflammation by Localizing Mononuclear Infiltrates to the Perivascular Space during Experimental Autoimmune Encephalomyelitis | The Journal of Immunology*.
<https://www.jimmunol.org/content/177/11/8053.long>. Accessed 25 July 2021.
- Definition of Granulocyte - NCI Dictionary of Cancer Terms - National Cancer Institute*. 2 Feb. 2011, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/granulocyte.nciglobal,ncienterprise>.
- Definition of Leukocyte - NCI Dictionary of Cancer Terms - National Cancer Institute*. 2 Feb.

- 2011, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/leukocyte.nciglobal,ncienterprise>.
- Definition of Macrophage - NCI Dictionary of Cancer Terms - National Cancer Institute.* 2 Feb. 2011, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/macrophage.nciglobal,ncienterprise>.
- Definition of Neurodegenerative Disorder - NCI Dictionary of Cancer Terms - National Cancer Institute.*
<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/neurodegenerative-disorder>. Accessed 10 July 2021.
- Dhaiban, Sarah, et al. “<p>Targeting Chemokines and Chemokine Receptors in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis</P>.” *Journal of Inflammation Research*, vol. 13, Dove Press, Sept. 2020, pp. 619–33.
www.dovepress.com, <https://doi.org/10.2147/JIR.S270872>.
- Dilokthornsakul, Piyameth, et al. “Multiple Sclerosis Prevalence in the United States Commercially Insured Population.” *Neurology*, vol. 86, no. 11, Mar. 2016, pp. 1014–21.
PubMed Central, <https://doi.org/10.1212/WNL.0000000000002469>.
- “Endothelial Function Testing.” *Cedars-Sinai*,
<https://www.cedars-sinai.org/programs/heart/clinical/womens-heart/services/endothelial-function-testing.html>. Accessed 19 Sept. 2021.
- Gaillard, Frank. “Perivascular Spaces | Radiology Reference Article | Radiopaedia.Org.” *Radiopaedia*, <https://radiopaedia.org/articles/perivascular-spaces?lang=us>. Accessed 19 Sept. 2021.
- Ghezzi, Laura, et al. “T Cells Producing GM-CSF and IL-13 Are Enriched in the Cerebrospinal Fluid of Relapsing MS Patients.” *Multiple Sclerosis Journal*, vol. 26, no. 10, SAGE Publications Ltd STM, Sept. 2020, pp. 1172–86. *SAGE Journals*,
<https://doi.org/10.1177/1352458519852092>.
- GM-CSF Production by Autoreactive T Cells Is Required for the Activation of Microglial Cells and the Onset of Experimental Autoimmune Encephalomyelitis | The Journal of Immunology.* <https://www.jimmunol.org/content/178/1/39>. Accessed 3 Aug. 2021.
- Hartmann, Felix J., et al. “Multiple Sclerosis-Associated IL2RA Polymorphism Controls GM-CSF Production in Human TH Cells.” *Nature Communications*, vol. 5, no. 1, Oct.

- 2014, p. 5056. *www.nature.com*, <https://doi.org/10.1038/ncomms6056>.
- Hoornaert, Chloé. *Modulatory Potential Of The TH2 Cytokine Interleukin-13 On The Blood-Brain Barrier And On Immune Cells In Multiple Sclerosis*.
<https://plan.core-apps.com/actrims2020/abstract/0a189cd9-9ce4-4676-9c5c-b8ae539519f0>. Accessed 9 July 2021.
- Intracrine - an Overview | ScienceDirect Topics*.
<https://www.sciencedirect.com/topics/neuroscience/intracrine>. Accessed 19 Sept. 2021.
- Lees, Jason R., and Anne H. Cross. “A Little Stress Is Good: IFN- γ , Demyelination, and Multiple Sclerosis.” *Journal of Clinical Investigation*, vol. 117, no. 2, Feb. 2007, pp. 297–99. *PubMed Central*, <https://doi.org/10.1172/JCI31254>
- Lotfi, Noushin, et al. “Roles of GM-CSF in the Pathogenesis of Autoimmune Diseases: An Update.” *Frontiers in Immunology*, vol. 0, Frontiers, 2019. *Frontiers*, <https://doi.org/10.3389/fimmu.2019.01265>.
- Luo, Qiong, et al. “Blocking Initial Infiltration of Pioneer CD8(+) T-Cells into the CNS via Inhibition of SHP-2 Ameliorates Experimental Autoimmune Encephalomyelitis in Mice.” *British Journal of Pharmacology*, vol. 171, no. 7, Apr. 2014, pp. 1706–21. *PubMed*, <https://doi.org/10.1111/bph.12565>.
- Martins, Thomas B., et al. “Analysis of Proinflammatory and Anti-Inflammatory Cytokine Serum Concentrations in Patients With Multiple Sclerosis by Using a Multiplexed Immunoassay.” *American Journal of Clinical Pathology*, vol. 136, no. 5, Nov. 2011, pp. 696–704. *Silverchair*, <https://doi.org/10.1309/AJCP7UBK8IBVMVNR>.
- McCandless, Erin E., et al. “IL-1R Signaling within the CNS Regulates CXCL12 Expression at the Blood-Brain Barrier and Disease Severity during Experimental Autoimmune Encephalomyelitis.” *Journal of Immunology (Baltimore, Md. : 1950)*, vol. 183, no. 1, July 2009, pp. 613–20. *PubMed Central*, <https://doi.org/10.4049/jimmunol.0802258>.
- “Meninges | Anatomy.” *Encyclopedia Britannica*, <https://www.britannica.com/science/meninges>. Accessed 19 Sept. 2021.
- Microvasculature - an Overview | ScienceDirect Topics*.
<https://www.sciencedirect.com/topics/immunology-and-microbiology/microvasculature>. Accessed 19 Sept. 2021.
- “Multiple Sclerosis.” *Nhs.Uk*, 23 Oct. 2017, <https://www.nhs.uk/conditions/multiple-sclerosis/>.

Neuroimmunology of the Interleukins 13 and 4.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4931495/>. Accessed 9 July 2021.

Ocrelizumab | Multiple Sclerosis Society UK.

<https://www.mssociety.org.uk/research/explore-our-research/emerging-research-and-treatments/explore-treatments-in-trials/ocrelizumab>. Accessed 19 Sept. 2021.

Optic Neuritis in MS: Symptoms, Causes, and Treatment. 13 June 2019,

<https://www.medicalnewstoday.com/articles/325460>.

Pathological Expression of CXCL12 at the Blood-Brain Barrier Correlates with Severity of

Multiple Sclerosis - PubMed. <https://pubmed.ncbi.nlm.nih.gov/18276777/>. Accessed 25 July 2021.

Phillips, Ceri J. “The Cost of Multiple Sclerosis and the Cost Effectiveness of

Disease-Modifying Agents in Its Treatment.” *CNS Drugs*, vol. 18, no. 9, 2004, pp. 561–74. *PubMed*, <https://doi.org/10.2165/00023210-200418090-00002>.

“Plasmapheresis: Plasma Exchange for MS.” *WebMD*,

<https://www.webmd.com/multiple-sclerosis/plasma-exchange-ms>. Accessed 19 Sept. 2021.

“Primary Progressive MS (PPMS).” *National Multiple Sclerosis Society*,

<https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS>. Accessed 17 July 2021.

Rao, S. M., et al. “Cognitive Dysfunction in Multiple Sclerosis. II. Impact on Employment and

Social Functioning.” *Neurology*, vol. 41, no. 5, May 1991, pp. 692–96. *PubMed*, <https://doi.org/10.1212/wnl.41.5.692>.

“Relapsing-Remitting MS (RRMS).” *National Multiple Sclerosis Society*,

<https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS>. Accessed 17 July 2021.

Schwann Cell - an Overview | ScienceDirect Topics.

<https://www.sciencedirect.com/topics/neuroscience/schwann-cell>. Accessed 11 July 2021.

“Secondary Progressive MS (SPMS).” *National Multiple Sclerosis Society*,

<https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS>. Accessed 17 July 2021.

Six Cost Drivers of Multiple Sclerosis.

<https://www.optum.com/business/resources/library/ms-cost-drivers.html>. Accessed 9 July 2021.

Tau, G., and P. Rothman. “Biologic Functions of the IFN- γ Receptors.” *Allergy*, vol. 54, no. 12, Dec. 1999, pp. 1233–51. *PubMed Central*,

<https://doi.org/10.1034/j.1398-9995.1999.00099.x>.

“The Immune System and Multiple Sclerosis.” *MSAA*, 16 Dec. 2015,

<https://mymsaa.org/ms-information/overview/immune-system/>.

The Spinal Cord | Boundless Anatomy and Physiology.

<https://courses.lumenlearning.com/boundless-ap/chapter/the-spinal-cord/>. Accessed 26 Sept. 2021.

“What Are Progenitor Cells? Exploring Neural, Myeloid and Hematopoietic Progenitor Cells.”

Cell Science from Technology Networks,

<https://www.technologynetworks.com/cell-science/articles/what-are-progenitor-cells-exploring-neural-myeloid-and-hematopoietic-progenitor-cells-329519>. Accessed 19 Sept. 2021.

“What Is a Neuron? Function, Parts, Structure, Types, and More.” *Healthline*, 20 July 2018,

<https://www.healthline.com/health/neurons>.

“What You Should Know About Treating Multiple Sclerosis Flare-Ups with Steroids.”

Healthline, 27 Feb. 2021, <https://www.healthline.com/health/steroids-for-ms>.

“WHIM Syndrome.” *NORD (National Organization for Rare Disorders)*,

<https://rarediseases.org/rare-diseases/whim-syndrome/>. Accessed 19 Sept. 2021.

White Matter of the Brain: MedlinePlus Medical Encyclopedia.

<https://medlineplus.gov/ency/article/002344.htm>. Accessed 26 Sept. 2021.

WIESEMANN, E., et al. “Correlation of Serum IL-13 and IL-5 Levels with Clinical Response to

Glatiramer Acetate in Patients with Multiple Sclerosis.” *Clinical and Experimental Immunology*, vol. 133, no. 3, Sept. 2003, pp. 454–60. *PubMed Central*,

<https://doi.org/10.1046/j.1365-2249.2003.02238.x>.

Zhang, Jun-Ming, and Jianxiong An. “Cytokines, Inflammation and Pain.” *International*

Anesthesiology Clinics, vol. 45, no. 2, 2007, pp. 27–37. *PubMed Central*,

<https://doi.org/10.1097/AIA.0b013e318034194e>

The Electric Eel. A Novel Line of Thought? by Avyakta Voruganti

It does what?!

Of all the weird and wonderful species on planet Earth that have managed to evolve themselves from single cells, the electric eel is amongst the most mind-blowing animals this world has to offer. And yet so little is understood about how it uses electricity to hunt prey, mate, and defend itself.

Despite its name, the electric eel isn't really an eel - it's a species of knife fish! Electric eels dwell in both saltwater and freshwater habitats drifting silently through the shallow water of the Amazon River basin... in the hunt for their next meal.

The electric eel isn't your average Joe in terms of how it hunts. They have a peculiar method of hunting, involving large amounts of electricity and tiny unsuspecting prey. The eel uses a high voltage pulse of electricity to stun its prey, after which it promptly gobbles them up. The real question here, however, is - how does it generate this burst of electricity, without a battery or any of the electrical components we use to do the same?

In this article, I'll be going into depth about the way these mysterious creatures find and catch their prey.

The electric eel has three organs that help it create its characteristic shocks: the Hunter's Organ, the Sachs Organ and the Main Organ - each of them have their own special role to play. The Hunter's organ and the Main Organ produce high voltage pulses of electricity meant to stun and then kill their prey. On the other hand, since the electric eel doesn't have great eyesight and can't rely solely on it to navigate the murky waters amongst the reeds - the Sachs Organ generates a low voltage pulse - meant only to help the eel orient itself, much like the echolocation used by bats and dolphins to communicate. But, once again, we are left wanting to know how these organs help in generating electricity.

The Answer To The Big ‘Question’

Each of these organs are packed tightly with specialized cells called electrocytes. They usually possess a rectangular shape with 4 membranes, like the sides of a rectangle. In this article, we will focus mainly on the polar changes occurring only around two of these sides (the ones opposite each other). The electrocytes are arranged with these two membranes facing their neighbor's membrane. Electrocytes can generate a potential difference across the membrane and reverse it just as quickly. While the eel isn't using its electricity, the electrocytes maintain a potential by pumping positively charged ions out of the cell, making the inside a lot more negative than the outside. This occurs across both the membranes of the cell.

To form an analogy- the membranes of electrocytes within each organ can be compared to a group of professional tug-of-war player. Imagine an electrocytes- one of its membranes are like half of a tug of war team and the other membrane is the other half One electrocyte would mak up the entire team. However, this team is an uncoordinated one and while half the players are pulling in the direction they are supposed to, the other half mindlessly tug in the exact opposite. Their uncoordinated efforts cancel each other out and lead to no actual change, that is, until their coach who was watching from the sidelines this whole time gives them the signal to start working together. Miraculously, half the team turn and start pulling in the other direction. Their strengths add up and they are able to win the game in a matter of seconds. Similarly, when the eel wants to release a burst of electricity, the signal reaches the electrocytes in the form of a neurotransmitter called Acetylcholine. If the entire team had reversed their positions, instead of only half of them, one half of the team would still be pulling in the wrong direction. In terms of the electrocyte, the catch is to make sure that the charges switch along only one of the membranes, for each of the electrocytes.

This would make one membrane positive and the other negative, in an alternating fashion. What does this remind you of? That's right! It's a battery! Now the eel has a power source with which it can deliver its shock! Since all the cells are very tightly packed together, they all switch their membrane polarity almost instantly.

Once this happens, the whole eel itself becomes a giant battery, with the positive pole near its head and the negative one in the Sachs Organ. This allows the eel to conduct its current

effectively in the water. When the eel needs to generate a more potent strike than usual, it can bend its body in the shape of a U, such that the positive and negative poles of the ‘battery’ are much closer to each other which provides a shorter path for a large amount of current to flow through. One can only feel sorry for any unsuspecting prey that happens to be between those poles.

However, in all this, one question remains unanswered: How does the eel not shock itself in the process? Although it seems very silly, the eel has no anti measures to protect itself from its own medicine. It simply makes sure that the poles of its body don’t touch each other, to ensure the circuit doesn’t short itself, making over 600V of electricity flow through the eels body, leaving it no better off than one of its prey.

Conclusion

In conclusion, the eel uses three organs to first, scout the area for prey, locate them and then move in for their killer strike. Each of these organs are packed with specialized cells called electrocytes which, when stimulated by the release of neurotransmitter acetylcholine reverses the membrane potential along only one of the membranes which makes every single cell behave like a battery, stacked up, (much like a Voltaic Stack) their tiny membrane potentials adding up to a whopping 600V of electricity! The electric eel directs this burst of electricity using its own body (which just so happens to become a gigantic battery.)

Our ‘Bright’ Future

The electric eel is one of the myriad wonders of the world and one that has always had my curiosity and doubtlessly those of countless others. Even to this day it remains a mystery and we can only hope to learn more about it in the future so that we can one day find a way to produce sustainable sources of energy, similar to how the eel produces electricity. I have always dreamed of a world based on sustainable sources of energy, one that can last our civilization eons to come, unlike the few years our unchecked use of fossil fuels and non-renewable fuels will. Therefore, thinking of new ways to realize this dream has always been a passion of mine. The electric eel is just one of millions of paths we can go down in search of sustainable sources of

energy, but one, I'm sure, will inspire an entirely new way of looking at the climate crisis, encouraging our generation to pull ourselves out of the pit we have dug ourselves into.

Strategies of Functionalizing CB[n] and Their Applications by Shangheng Zhong

Introduction

Supramolecular chemistry is the study of non-covalent interactions between molecules^[1]. Macrocycles are a class of molecule studied in supramolecular chemistry and they show great potential in different areas such as forming a variety of host-guest complexes, molecular probes, and as drug carriers^[2,5,6]. Typical examples of macrocyclic molecules are crown ethers, cyclodextrins (CD), calixarenes, and pillararenes^[2]. These macrocycles interact with guest molecules through different intermolecular forces such as hydrogen bonding, pi-pi stacking, ion-dipole interactions, metal-ligand interactions, and through the hydrophobic effect. The strength of different intermolecular forces are shown below in Table 1.

Force/Interaction	Strength	Characteristics
Hydrogen Bond	Typical strength of 2-15 Kcal mol ⁻¹	Directional
Pi Stacking	10 Kcal mol ⁻¹ [4]	Directional
Ion-Dipole Interaction		Non-Directional
Metal-ligand Interaction		Directional
Hydrophobic Effect		Non-Directional

Table 1. Strength and characteristics of different intermolecular forces/interactions

Cucurbituril (CB) is a macrocyclic molecule consisting of glycoluril subunits linked together through methylene bridges. The class of macrocycles was named “cucurbituril” as the molecules look like ‘pumpkins’, which belongs to the *Cucurbitaceae* family of squash/gourd^[7]. Cucurbituril was first synthesized by Behrend and his student in the early 20th century and reported in a PhD thesis and then in a peer-reviewed journal in 1905^[8], however, the structure remained unknown and Behrend only obtained a molecular formula of C₁₈H₁₈N₁₂O₆. In 1981, the structure was determined by Mock *et al.*^[9], which is known as

CB[6] today (structure shown in Fig 1(a) and 1(b)), the number 6 in the square brackets represents the number of glycoluril subunits present in the cucurbit[6]uril macrocycle. The molecular formula obtained by Behrend is consistent with the structure determined by Mock ($(C_6H_6N_4O_2)_n$). After the structure of CB[6] was determined, studies continued over the next 2 to 3 decades. In 1983, Mock and Shih investigated host-guest binding between CB[6] and a range of alkylammonium ions. They reported that 1,6-hexanediammonium ion ($HN^+_3-(CH_2)_6-NH_3^+$) forms the most stable host-guest complex with CB[6]. Mock inferred that there is a charge-dipole interaction between the ammonium ions and the oxygen-lined portals of CB[6]^[10]. In 1992, Buschmann and co-workers studied complexes that formed between CB[6] and inorganic cations, their results suggest that inorganic cations generally form more stable complexes with CB[6] than with a ubiquitous crown ether (18-crown-6)^[11]. In 2000, Kim *et al.* synthesized and isolated a range of CB homologues: CB[5], CB[7] and CB[8]. X-ray crystallography confirmed that each CB homologue has a distinct portal and cavity diameter^[12]. This was an important point in the field as different cavity and portal sizes would have a substantial effect on the binding properties of each CB homologue.

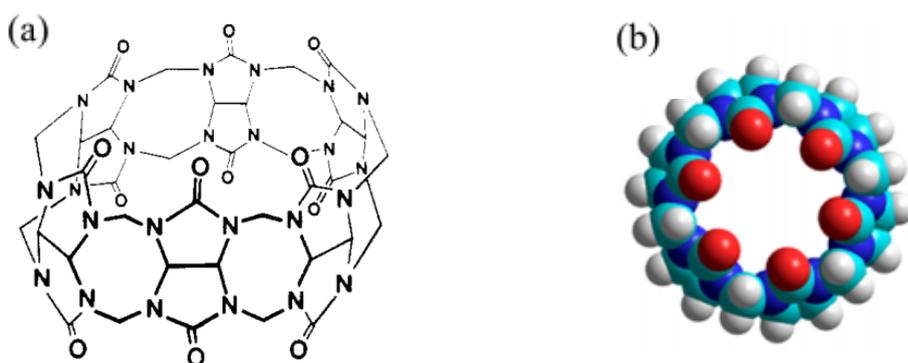


Fig 1. (a) Structural formula of CB[6]^[10] and (b) space-filling model of CB[6]^[7].

There are several unique characteristics of CB macrocycles. Firstly, they have high stability, CBs have a rigid structure^[10,13,14]. In addition, CBs have high chemical and heat stability, CBs rarely undergo chemical reactions, and they can withstand temperatures up to 425 ° C without severe decomposition (minor decomposition starts at 250 ° C, potentially being the release of trapped water molecules inside)^[15]. Furthermore, they have low solubility in water and are virtually insoluble in organic solvents (solubilities of CB[n] homologues are

summarized in Table 2)^[16], which is a major drawback to CB chemistry as many chemical reactions are carried out in organic solvents, hence limiting the potential for CB functionalization. In addition, toxicological studies of CBs suggest that CB has low toxicity towards a variety of human cells. Hettiarachchi *et al.* studied the toxicity of CB[5] and CB[7] on human liver cells (HepG2) and human kidney cells (HEK 293). The results suggest only 9% and 11% cell death (HEK 293) after 48 h incubation of 1 mM CB[5] and CB[7], respectively, which were lower than that of the positive control (18% cell death)^[6]. A similar phenomenon was witnessed for HepG2. Another study conducted by Jeon *et al.* suggests that CB[7] shows no cytotoxic effect towards A549 human non-small lung cells, SKOV-3 human ovarian, SKMEL-2 human melanoma, XF-498 human CNS, and HCT-15 human colon cells^[17]. This is an exciting result as low toxicity implies that CBs have potential in *in-vivo* applications such as drug delivery. However, these toxicology studies were performed in *in-vitro* environments. Further *in-vivo* study is needed in order to ensure CBs are safe for use in the human body.

CB[n]	Solubility (mg/L)
CB[5]	30
CB[6]	18
CB[7]	30
CB[8]	.01
CB[10]	.01

Table 2. Water solubility of different CBs^[16]

Researchers may wish to functionalize CBs for several reasons, such as improving their solubility in water and organic solvents and endowing CBs with unique molecular recognition capabilities. Additionally, applications of functionalized CBs are further elaborated in part 3 of this review.

Unfortunately, although functionalization of CBs brings many advantages, it is difficult to functionalize CBs compared to other macrocyclic compounds. There are two reasons for

this: firstly, as mentioned above, CB is insoluble in organic solvents, which prohibits many potential chemical reactions for functionalization of CBs. In contrast, pillararene is soluble in different conventional organic solvents like chloroform, dichloromethane, DMF, and pyridine. This solubility in organic solvents allows pillararene to undergo various chemical reactions such as coupling reactions and nucleophilic substitutions^[2]; cyclodextrin also shows solubility in DMF and THF^[18,19], which allows versatile chemical reactions to take place. Secondly, CB does not have reactive functional groups for subsequent reactions. In contrast, reactive functional groups are present in other macrocyclic compounds, such as phenol groups in pillararene and calixarenes and hydroxyl groups in cyclodextrin. These reactive functional groups readily allow for subsequent reactions to take place. In this review, different strategies for functionalization of CBs will be summarized and compared, additionally, applications of functionalized CBs will be discussed. This review provides readers with a general understanding of the different approaches that have been used for functionalization of CBs and their potential applications.

Synthetic Strategies of Functionalization of CB

In general, there are three strategies to functionalize CB: functionalization by using substituted glycoluril, functionalization by using glycoluril diether, and functionalization by oxidation.

Functionalization by Using Substituted Glycoluril

As CB is formed by condensation reaction between glycoluril and formaldehyde, functionalization of CB is possible by modifying monomer of CB (glycoluril). Synthesis of substituted glycoluril is achieved by condensation reaction between α , β -diketone, and urea^[20] (shown in Fig 2)

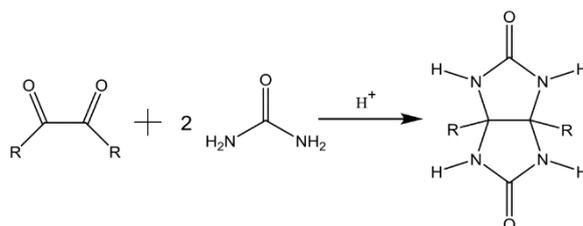


Fig 2. Synthesis of substituted glycoluril^[20]

Although it is difficult to functionalize CB directly, it is easier to synthesize substituted glycoluril. Researchers can add simple substituents on the equator of glycoluril, and hence, CB synthesized from substituted glycoluril would be functionalized. In 1992, Stoddart *et al.* reported the synthesis of decamethylcucurbit[5]uril ($\text{Me}_{10}\text{CB}[5]$, structure shown in Fig 3) by reacting methyl substituted glycoluril and formaldehyde under acidic conditions. X-ray crystallography data of $\text{Me}_{10}\text{CB}[5]$ suggest that N-C-N (C refer to the carbon in methylene bridge) angle is between 114° to 116° , which is different from ordinary value of 109° . Stoddart deduced the fact that deviation in bond angle is caused by molecular strain created by methyl groups on the equator^[21]. This strain may also explain the low yield of this reaction (16%). Other functionalized CB homologues may also form in this reaction. Nevertheless, the yield is extremely low. In 2004, Keinan and co-workers isolated dodecamethylcucurbit[6]uril ($\text{Me}_{12}\text{CB}[6]$) from the reaction mixture of methyl substituted glycoluril and formaldehyde by affinity chromatography and yield of $\text{Me}_{12}\text{CB}[6]$ was only 0.2%^[22]. Other than glycoluril substituted by two methyl group, glycoluril substituted with only one methyl group and corresponded functionalized CB is also synthesized. In 2008, Tao *et al.* reported the synthesis of $\text{Me}_n\text{CB}[n]$ ($n=5,6,7$) by adopting monomethyl-substituted glycoluril as a monomer. These products show better solubility compare to that of unfunctionalized CBs, and they are soluble in organic solvents. Interestingly, there are four potential isomers for $\text{Me}_5\text{CB}[5]$, nine for $\text{Me}_6\text{CB}[6]$, and ten for $\text{Me}_7\text{CB}[7]$ respectively. However, experimental results suggest that the product mixture is mainly consists of two isomers (shown in Fig 4). In order to explain this phenomenon, Lin obtained dipoles and ground energies for different isomers through *ab initio* calculation. The result of *ab initio* calculation shows that isomer 2 (see Fig 4(a)) has the highest dipoles among other isomers of $\text{Me}_5\text{CB}[5]$, a similar result is obtained for isomer 6 (see Fig 4(b)). This implies that isomer 2 and 6 might have the highest water solubility than other isomers do^[23].

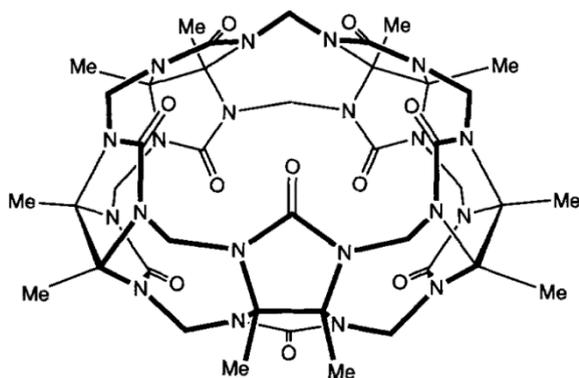


Fig 3. Structural formula of decamethylcucurbit[5]uril^[21]

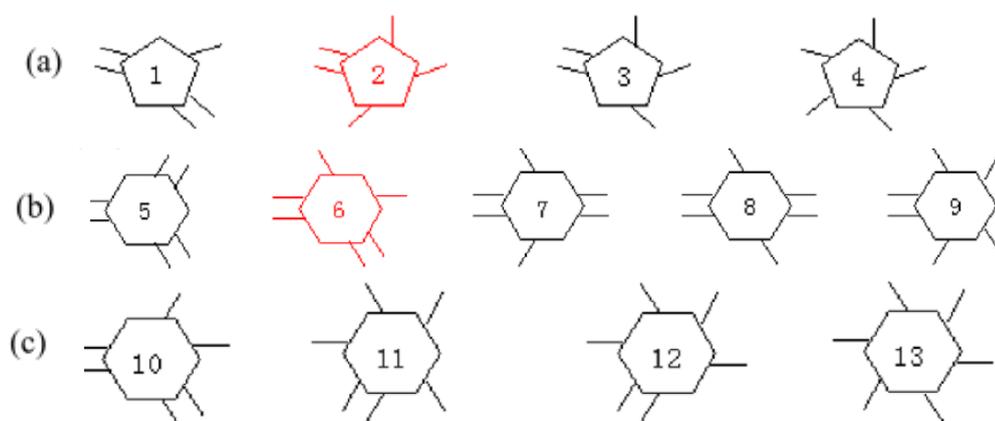


Fig 4. (a). potential isomers of Me₅CB[5] and (b, c). potential isomers of Me₆CB[6], major products are labeled with red color^[23]

Other than simple methyl group, cycloalkyl group can also be added on glycoluril and form correspond functionalized CB in subsequent reaction. In 2001, Kim *et al.* reported the synthesis of CB[5] and CB[6] functionalized with cyclohexyl group at the equator (Cy₅CB[5] and Cy₆CB[6]) by reacting cyclohexyl substituted glycoluril and formaldehyde (shown in Fig 5). A similar phenomenon in the synthesis of Me₁₀CB[5] is also witnessed in the synthesis of Cy_nCB[n] that functionalized CB[5] is the major product of the reaction. Similar to Me_nCB[n], these functionalized CBs also exhibit better solubility in water and some solubility in some organic solvents such as DMSO^[24]. Enhancement in solubility in organic solvent of functionalized CBs suggests that

substituents play a critical role in solvation of CBs.

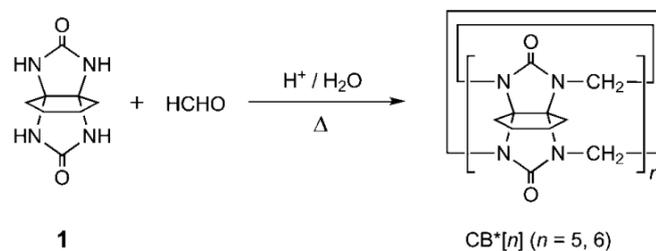


Fig 5. Synthesis of cyclohexyl-functionalized $\text{CB}[n]$ ^[24]

In 2015, Wang *et al.* reported the synthesis of $\text{CB}[5]$ analogue ($\text{Me}_{10}\text{TD}[5]$) using dimethylpropanediurea (Me_2TD) and paraformaldehyde (see Fig 5(a)) with 5% yield. Compared to other substituted glycoluril mentioned above, it has a propyl group inserted to the equator of glycoluril. Compared to unfunctionalized $\text{CB}[5]$, $\text{Me}_{10}\text{TD}[5]$ has a larger cavity diameter and lower height (cavity diameter and height of unfunctionalized $\text{CB}[5]$ are 4.4 Å and 9.1 Å respectively^[7]). These changes would obviously lead to different binding properties compared to that of $\text{CB}[5]$. Study on binding behavior of $\text{Me}_{10}\text{TD}[5]$ suggests that portal of $\text{Me}_{10}\text{TD}[5]$ exhibit good affinity towards ammonium ion and supramolecular polymer is formed by ion-dipole interaction between ammonium ion in 1,4-xylylene diamine hydrochloride and portals of $\text{Me}_{10}\text{TD}[5]$ (see Fig 5(b)). In addition, $\text{Me}_{10}\text{TD}[5]$ also has higher solubility in water and in organic solvents like other functionalized CBs ^[25].

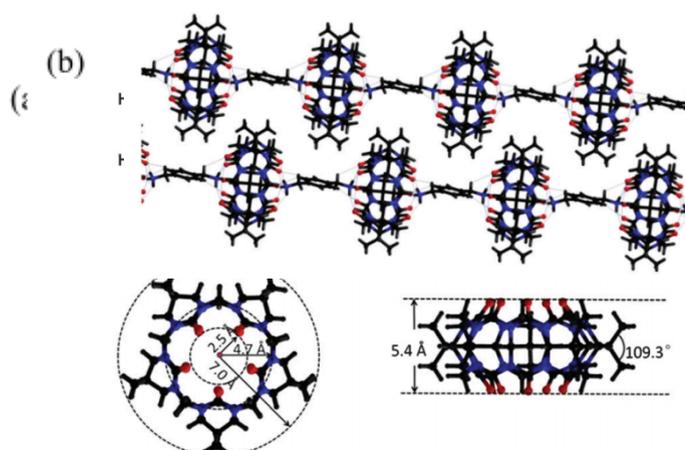


Fig 5. (a). Synthesis of Me₁₀TD[5] and (b). single crystal structure of supramolecular polymer between Me₁₀TD[5] and 1,4-xylene diamine hydrochloride^[25]

When the substituent gets larger, per-functionalized CB may not be able to be synthesized, instead, mono-functionalized CB might be obtained by adopting a mixture of substituted glycoluril and glycoluril as the monomer. In 2002, Nakamura and co-workers reported the synthesis of mono-functionalized (as there is only one substituted glycoluril subunit in CB) CB[6] (Ph₂CB[6]) by mixing diphenyl-substituted glycoluril and unsubstituted glycoluril as the monomer (shown in Fig 6). Products consisted of both Ph₂CB[6] and unfunctionalized CB[6]. Isobe and co-workers attempted for dodecasubstituted CB[6], but unfortunately, the attempt was unsuccessful. Isobe believed that the unsuccessful attempt is caused by steric hindrance created by phenyl group, which prohibits the formation of substituted glycoluril hexamer^[26].

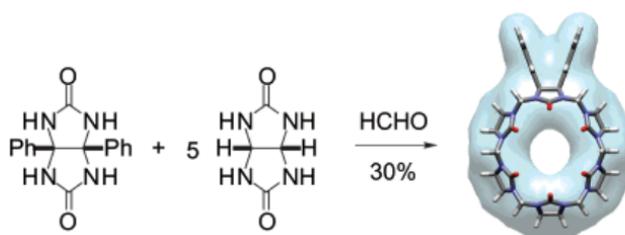


Fig 6. Synthesis of Ph₂CB[6]

Functionalization by Using Glycoluril Diether

Glycoluril diether is synthesized from substituted glycoluril (shown in Fig 7). In practice, glycoluril diether act as a monomer in the synthesis of functionalized CB. People usually use glycoluril diether along with glycoluril oligomer. By choosing the appropriate glycoluril oligomer, a variety of functionalized CB can be synthesized.

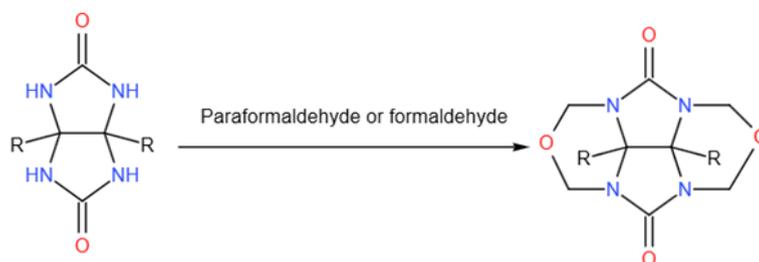


Fig 7. Synthesis of glycoluril diether

In 2004, Xue *et al.* reported the synthesis di-functionalized CB[6] ($\text{Me}_4\text{CB}[6]$, see Fig 8) by reacting dimethylglycoluril diether and glycoluril dimer. Surprisingly, $\text{Me}_4\text{CB}[6]$ is ellipsoid instead of circular^[27]. Two methyl-substituted glycoluril subunits are located in the opposite position in $\text{Me}_4\text{CB}[6]$. This $\text{Me}_4\text{CB}[6]$ can also express as [dimethyl-substituted glycoluril diether-glycoluril dimer-diether-glycoluril dimer]. Since there is no additional formaldehyde is added to the reaction between dimethylglycoluril diether and glycoluril dimer, it is reasonable to deduce that function of the diether group is to create linkage between glycoluril dimer and substituted glycoluril. Glycoluril dimer will not joint together to form unfunctionalized CB, as there is no formaldehyde in the system, and fully-functionalized CB (such as $\text{Me}_{12}\text{CB}[6]$) is not favorable as methyl group would create additional strain to CB^[21]. Hence, a more favorable route is to form a symmetry di-functionalized CB[6] shown in Fig 8. Such a high selectivity would not be achieved by mixing dimethylglycoluril, glycoluril, and formaldehyde together, because there are many potential products that would be formed ($\text{CB}[5,6,7]$, $\text{Me}_2\text{CB}[5,6,7]$, $\text{Me}_4\text{CB}[5,6,7]$...).

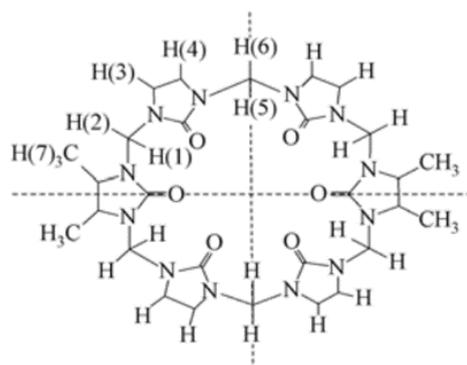


Fig 8. Structure of Me₄CB[6]^[27]

In 2012, Issacs *et al.* reported the synthesis of a range of mono-functionalized CB[7]s by reacting glycoluril hexamer and substituted glycoluril diether. These substituents include methyl group and cyclohexyl group. There are also substituted glycoluril diether with two different substituents like methylphenylglycoluril diether. Furthermore, when one of the substituents is haloalkane, azide group can be introduced to the functionalized CB[7] by substitution reaction. This azide group may further react with alkyne to form triazole (shown in Fig 9(a)). Since triazole has the potential to form a host-guest complex with CB, this functionalized CB[7] may form a self-assembled complex. In this scenario self-assembled functionalized CB[7] tetramer is formed (shown in Fig 9(b))^[28]. It is noticeable that Issacs reported the formation of unfunctionalized CB[6], which is not reported in reference [27]. A potential reason might be the decomposition of glycoluril diether in the reaction yield free formaldehyde leading to cyclization of glycoluril hexamer.

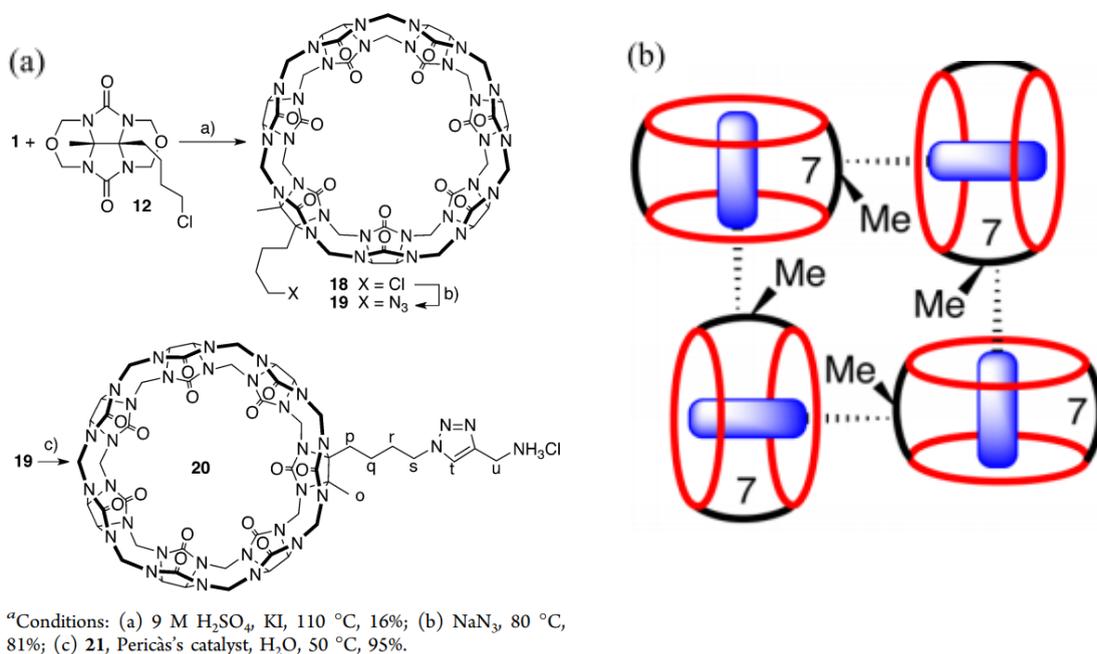


Fig 9(a). synthesis of functionalized CB[7] with triazole group and (b) self-assembled CB[7] tetramer

Fully-functionalized CB can form by reacting substituted glycoluril diether and substituted glycoluril dimer. In 2021, Tao *et al.* reported the synthesis of dodecamethylcurbit[6]uril ($\text{Me}_{12}\text{CB}[6]$) by reacting dimethylglycoluril diether and methyl-substituted glycoluril dimer, the product formed is a mixture of $\text{Me}_{10}\text{CB}[5]$ and $\text{Me}_{12}\text{CB}[6]$. Although the major product is $\text{Me}_{10}\text{CB}[5]$, they also obtained $\text{Me}_{12}\text{CB}[6]$ in the yield of 4%. It is much better than 0.2% yield by reacting methyl-substituted glycoluril with formaldehyde^[22].

Although examples mentioned above synthesized functionalized CB by mixing substituted glycoluril diether and glycoluril oligomer, functionalized CBs can also form using glycoluril diether solely. In 2017, Zhao reported the synthesis of cyclobutanocurbit[n]uril ($\text{CyB}_n\text{CB}[n]$) by heating cyclobutanoglycoluril diether under acidic conditions. Analysis of the product suggests that it contains different CB homologues from $\text{CyB}_5\text{CB}[5]$ to $\text{CyB}_8\text{CB}[8]$, and $\text{CyB}_5\text{CB}[5]$ and $\text{CyB}_6\text{CB}[6]$ are the major products of this reaction. The author also synthesized furanocurbit[n]uril by using the similar method. Unfortunately, the separation of furanocurbit[n]uril was unsuccessful. The formation of furanocurbit[n]uril is proven by $^1\text{H NMR}$ ^[20]. Summary of synthesis of cyclobutanocurbit[n]uril and furanocurbit[n]uril is shown in Fig 10.

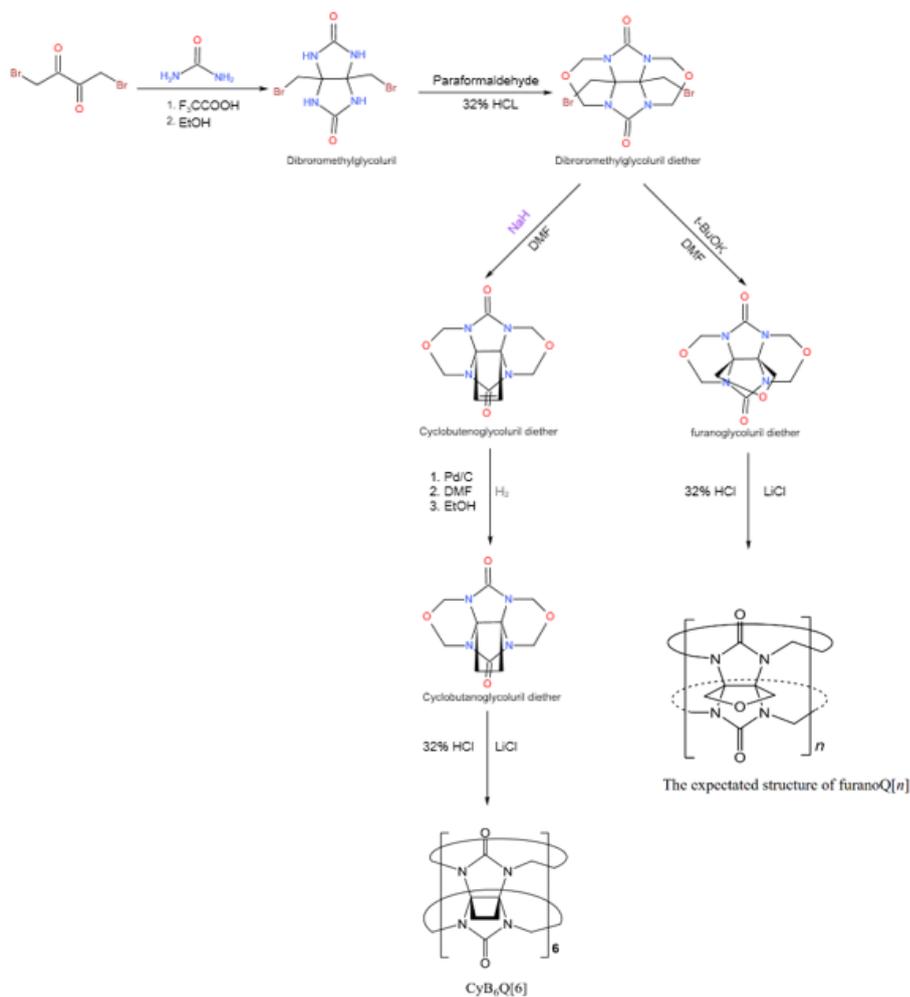


Fig 10. Summary of synthetic route of cyclobutanocucurbit[n]uril and furanocucurbit[n]uril (picture of cyclobutanocucurbit[n]uril and furanocucurbit[n]uril are adopt from ref [20], the author uses Q to represent CB)

Functionalization by Oxidation

One difference between the oxidation method and previous two methods is that functionalization by oxidation does not require any glycoluril derivatives, instead, it works on entire CBs. In 2003, Kim *et al.* reported the synthesis of perhydroxycucurbit[5-8]uril (shown in Fig 11(a)) by reacting CB[5-8] with K₂S₂O₈. An additional hydroxyl group is

added on carbons at the equator of glycoluril subunit. perhydroxycucurbit[6]uril ((HO)₁₂CB[6]) exhibits solubility in organic solvents like other functionalized CB do. Although the mechanism of this reaction remains unclear, Kim and co-workers deduced that hydroxyl radical is involved in this reaction^[30]. In 2012, Scherman and co-workers reported the synthesis of mono-hydroxylated CB[6] ((HO)₂CB[6]) using (NH₄)₂S₂O₈ as an oxidant. Compare to K₂S₂O₈, (NH₄)₂S₂O₈ has higher solubility in water and lower binding affinity towards carbonyl portal of CB. Scherman and co-workers also investigated the effect of different dosage of ammonium persulphate on the formation of different hydroxylated CB[6], the result suggests that when CB[6]: (NH₄)₂S₂O₈ is 1:1 the product mainly consist of (HO)CB[6] and (HO)₂CB[6] with the minority of (HO)₃CB[6] formed. When (NH₄)₂S₂O₈:CB[6] is 2.5:1 quantity of (HO)₃CB[6] formed increase significantly with a small amount of (HO)₄CB[6] formed^[31]. In 2017, Kaifer *et al.* reported the synthesis of monohydroxylcucurbit[7]uril ((HO)CB[7], shown in Fig 11(b)) using ammonium persulphate. Compare to Scherman's method^[31], Kaifer add NaHSO₃ and yield of (HO)CB[7] increase after the addition of NaHSO₃. Kaifer conveys that formation of hydroxyl radical is promoted by redox reaction between NaHSO₃ and (NH₄)₂S₂O₈^[32]. When ratio of (NH₄)₂S₂O₈:CB increase, CB[7] with multiple hydroxyl group is also observed similar as Scherman's result^[31].

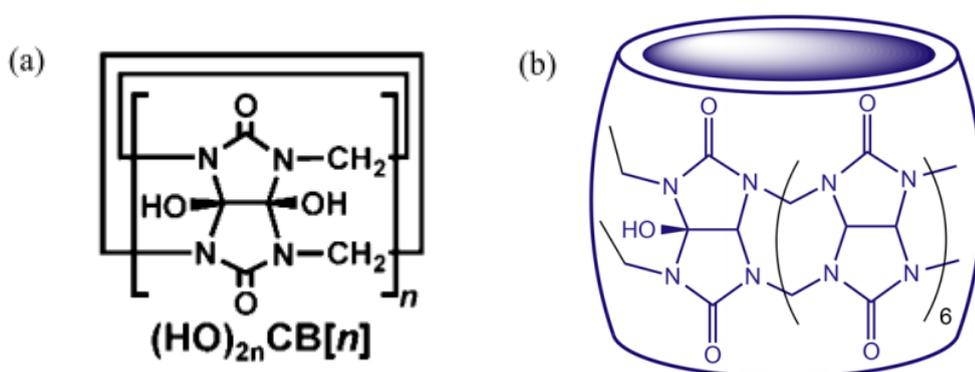


Fig 11(a). structure of perhydroxycucurbit[n]uril^[30]

(b). structure of mono-hydroxycucurbit[7]uril^[32]

Other than persulfate species, hydrogen peroxide can also act as the effective oxidant in

oxidation of CBs. In 2015, Bardelang *et al.* reported the synthesis of a range of monohydroxycucurbituril homologues ((HO)CB[5-8]) by using hydrogen peroxide as the oxidant. The reaction is catalyzed by UV light, and the degree of oxidation can be controlled by UV irradiation time. One of the advantages of using hydrogen peroxide as the oxidant is hydrogen peroxide would reduce to water, no additional ions would contaminate the system. Theoretical calculation suggests that carbon on the equator of glycoluril has the highest tendency to react with hydroxyl radical as tertiary radical has higher stability than that of secondary carbon^[33].

Hydroxycucurbit[n]uril is not the ultimate goal for CB functionalization. As hydroxyl group is a reactive functional group, subsequent functionalization can achieve by different reaction. Kim *et al.* introduced propionyl group and Allyl group on dihydroxycucurbit[6]uril ((HO)₂CB[6]) through nucleophilic substitution (shown in Fig 12(a))^[30]. Similarly, Scherman *et al.* introduced allyl group and propargyl group on monohydroxycucurbit[6]uril ((HO)CB[6]) by nucleophilic substitution^[31]. It is noticeable that these reactions are all carried out in DMSO, which is achieved by the solubility of hydroxycucurbit[n]uril in the organic solvent.

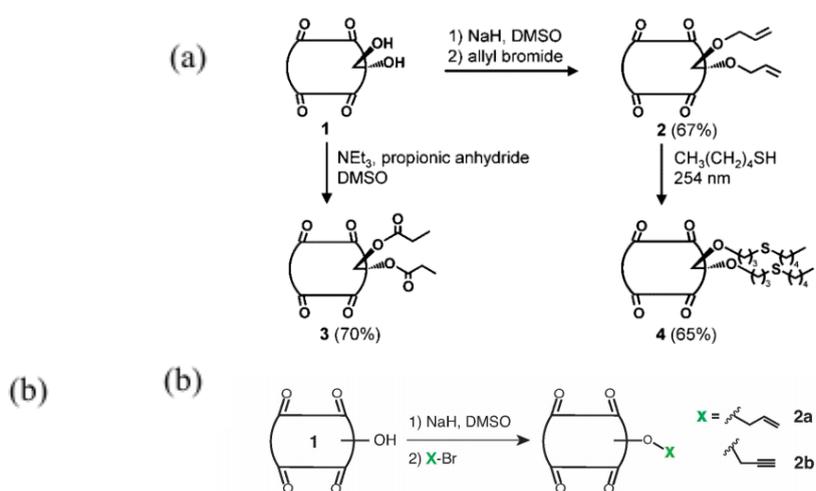


Fig 12(a) and (b). subsequent functionalization of hydroxycucurbit[6]uril^[30,31]

Summary and Comparison Between Different Strategies of Functionalization

Information of synthesis of different functionalized CB is summarized in Table 3.

Category	Reactant(s)	Reaction Conditions	Product(s)	Yield
Functionalization by substituted glycoluril	Me ₂ GU HCOH	HCl/H ₂ O Heating	Ph ₁₀ CB[5]	90% [21]
	CyGU HCOH	H ₂ SO ₄ 80 ° C	Ph ₅ CB[5] Ph ₆ CB[6]	90% 95% [24]
	Ph ₂ GU GU HCOH	(NH ₄) ₂ SO ₄ H ₂ SO ₄ 70 - 95 ° C	Ph ₄ CB[6] Ph ₃ CB[6]	90% 90% [26]
	Me ₂ GU HCOH	H ₂ SO ₄	Ph ₁₀ CB[5] Ph ₁₂ CB[6]	90% [22]
	MeGU Paraformaldehyde	HCl 90 ° C	Ph ₅ CB[5] Ph ₆ CB[6] Ph ₇ CB[7]	85% 83% 90% [23]
	Me ₂ TD (Fig 5(a)) paraformaldehyde	HCl 95 ° C	Ph ₁₀ TD ₅	90% [25]
	Functionalization by glycoluril Diether	Me ₂ GU diether GU dimer	HCl 100 ° C	Ph ₄ CB[6] (Fig 8)
Me ₂ GU diether GU hexamer		H ₂ SO ₄ 110 ° C	Ph ₂ CB[7]	90% [28]
CyGU diether GU hexamer		H ₂ SO ₄ 110 ° C	PhCB[7]	90% [28]
MePhGU diether GU hexamer		H ₂ SO ₄ 110 ° C	PhPhCB[7]	95% [28]
Me(BuCl)GU		H ₂ SO ₄	Ph(BuCl)CB[7](Fig 9)	90% [28]

	diether*	KI	CB[n]	
	GU hexamer	110 ° C		
	CyBGU diether**	32% HCl 95 ° C	B ₅₋₈ CB[5-8]	[20]
	FuranoGU diether (Fig 10)		Furano _n CB[n]	- [20]
	Me ₂ GU diether Me ₂ GU dimer	12M HCl 95 ° C	Me ₂ CB[6]	5% [21]
Functionalization by oxidation	CB[5-8] K ₂ S ₂ O ₈	H ₂ O 85 ° C	(O) _{10,12,14,16} CB[5-8]	42% 45% 5% 4% [30]
	CB[6] (NH ₄) ₂ S ₂ O ₈	H ₂ O 85 ° C	(O)CB[6] (O) ₂ CB[6]	9% [31]
	CB[5-8] H ₂ O ₂	UV (254nm)	(O)CB[5-8]	40% [34]
	CB[7] (NH ₄) ₂ S ₂ O ₈ NaHSO ₃	H ₂ O 65 ° C	(O)CB[7]	9% [32]

Table 3. summary of synthesis of different functionalized CB (Note. GU represent glycoluril, all substituents are located in carbon on the equator of glycoluril; *: BuCl refer to chlorobutyl group, check Fig 9(a) for more detail; **: CyB refer to cyclohexyl group, check Fig 10 for more detail)

In general, regardless which strategy of functionalization is adopted, the yield would decrease as the number of substituents presented in functionalized CBs increases, which is probably caused by substituent create strain on CBs^[21], making functionalized CBs less stable. Furthermore, when the size of the substituent gets larger, the yield of the reaction tends to decrease. For example, Me₂CB[7], CyCB[7] and MePhCB[7]-three functionalized CB[7] synthesized by Issacs and co-workers^[28]- have the yield of 31%, 18%, and 3%

respectively. Since these three functionalized CB[7] are synthesized in the same reaction conditions(see table 3), it is reasonable to deduce that larger substituent sizes cause a lower yield.

For functionalization by substituted glycoluril, it is a simple, straight-forward method to functionalized CB. However, it has several limitations: firstly, functionalized CBs synthesized under this approach are mainly functionalized CB[5] and CB[6]. In contrast, functionalized CB[7] and CB[8] species are synthesized by both oxidation method and glycoluril diether method(see table 3). Secondly, there are a limited number of substituents available. Substituent added on CBs by substituted glycoluril are simple functional group such as methyl group and phenyl group. More versatile functional group are able to introduce to CBs by other approaches, such as furanocucurbit[n]uril can be introduced to CB by using furanoglycoluril diether^[20], with respect to hydroxycucurbit[n]uril, variety of functional groups can add on CB by subsequent reaction like nucleophilic substitution.

For functionalization by glycoluril diether, functionalized CBs can be synthesized with high selectivity by using a combination of glycoluril diether and appropriate glycoluril/substituted glycoluril oligomers, for instance, di-functionalized CB[6] with a specific arrangement of substituted glycoluril (Me₄CB[6]^[27]). However, there is one drawback for this approach: there is one additional step to synthesized substituted glycoluril diether compare to that of simply substituted glycoluril. It may affect the overall yield of the synthesis.

Lastly, for functionalization by oxidation, it introduced a reactive hydroxyl group on CBs for subsequent reactions. In addition, as hydroxycucurbit[n]uril are soluble in organic solvents, subsequent reactions can take placed on those solvent. However, as free radical may involve in the process of oxidation, hydroxyl radical is highly reactive that reaction condition needs to control carefully to avoid formation of undesired product.

Applications of functionalized CB

As mentioned in the introduction of this review. Researchers may wish to functionalized CBs in order to modified the physical properties (solubility, cavity size) and provided

specific properties that unfunctionalized CBs do not have by introducing different functional group. In this chapter, these properties are discussed in detail.

Modifications of physical/Binding properties

The physical property that changes most dramatically is the solubility of CBs. Variety of functionalized CBs exhibit increase in water solubility^[23, 25, 27, 30, 31] as well as solubility in organic solvents^[23, 25, 27, 30, 31]. This widens the range of subsequent reactions that can take place. Surprisingly, the majority of functionalized CBs exhibit similar conformation with unfunctionalized CBs^[23, 28, 31] with some exception that molecule has ellipsoid conformation^[27]. Another example is Me₁₀TD[5], which has a significant lower height than conventional CB[5]^[7]

With respect to binding properties, binding properties of functionalized CBs and unfunctionalized CBs are similar^[28, 32]. Further study on binding properties is needed to have a deeper understanding on binding properties of functionalized CB.

Functionalization on surface

In 2003, after the discovery of oxidation of CBs using K₂S₂O₈, Kim and co-workers fabricated thiol-terminated glass slide with CB attachment (Shown in Fig 13). This is achieved by reacting allyl-functionalized CB[6] with glass slide with UV irradiation. This CB-attached glass slide can form complex with fluorescence guest and fluorescent is observed under Fluorescence microscope. It shows the potential in designing sensors and biochips^[30].

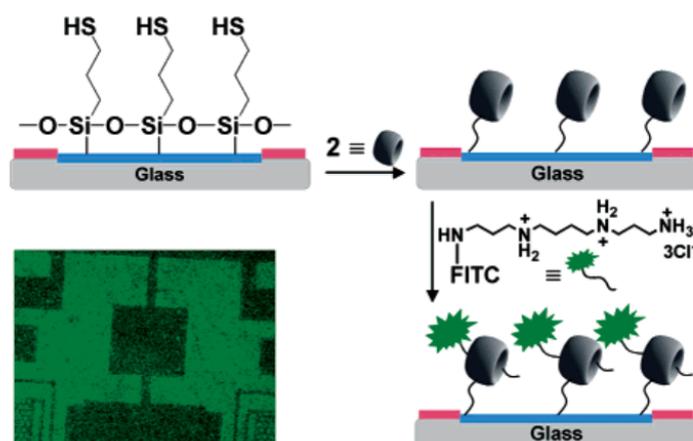


Fig 13. Fabrication of CB-attached glass slide and fluorescence microscopic image of glass slide after CB binds with fluorescence guest^[30]

Biological Applications

As CB shows low toxicity to human cell in *in vitro* toxicology studies. It shows its potential in various biological applications such as drug delivery, protein recognition, and 3D tissue engineered hydrogel. In 2013, Briken *et al.* reported the synthesis of biotinylate CB[7] for targeted delivery of oxaliplatin (shown in Fig 14). Biotin acts as targeting ligand of L1210DR cell. As the result oxaliplatin would be released after biotin binds to L1210DR. *in-vitro* experiment suggests that oxaliplatin encapsulated by biotinylate CB[7] takes much lower dosage to kill cancer cells compared to that of untreated oxaliplatin^[35]. In 2019, Wemmer *et al.* developed a biosensor for the detection of protein interaction. It consists of biotinylate CB[7] and xenon. Xenon is an atom that is capable to encapsulated by CB[7], when xenon is encapsulated by biotinylate CB[7] bound to avidin(avidin is a protein with 4 biotin receptor) ¹²⁹Xe hyperCETS NMR would give a signal at -40 ppm (shown in Fig 15). The existence of protein interaction can be determined by whether there is a signal at -40 ppm in NMR spectrum^[36]. In 2014, Park *et al.* reported the synthesis of 3D tissue engineered hydrogel consists of CB[6] functionalized with hyaluronic acid, diamino hexane conjugated hyaluronic acid and drug conjugated CB[6] (shown in Fig 16). This hydrogel exhibits the ability to release transforming growth factor- β 3 (TGF- β 3) and/or dexamethasone and it has the potential to become a platform for controlled drug delivery for cartilage regeneration^[37].

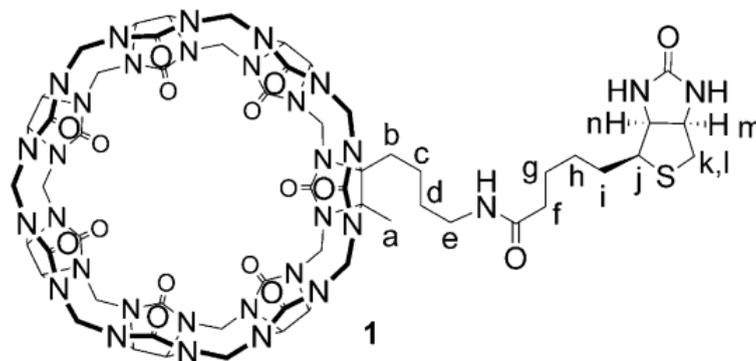


Fig 16. Schematic illustration of 3D tissue engineered hydrogel^[37]

Molecular Recognition

In 2021, Tao *et al.* constructed a $\text{Me}_{12}\text{CB}[6]/\text{ZnCl}_4^{2-}$ framework for selective accommodation of ortho-phenyl diamine (o-PDA). In solid state $\text{Me}_{12}\text{CB}[6]/\text{ZnCl}_4^{2-}$ framework would only accommodate o-PDA while other isomers will not be accommodated onto this framework. Authors deduced that only o-PDA would be trapped on this framework as it has the shortest length among other isomers. This might be useful to separate PDA isomers^[29].

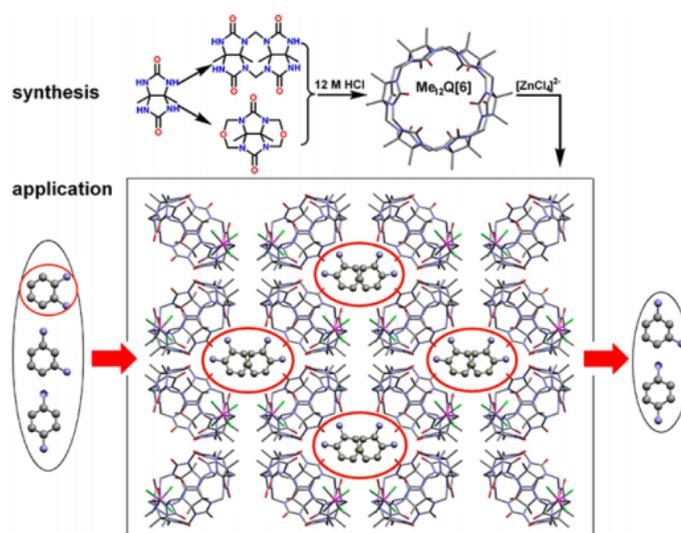


Fig 17. $\text{Me}_{12}\text{CB}[6]/\text{ZnCl}_4^{2-}$ framework for selective accommodation of o-PDA^[29]

Conclusion and Outlook

Overall, this review summarized different strategies in functionalization of CB as well as compared pros and cons of different strategies. This review also discussed the applications of a variety of different functionalized CB homologues. As people have gained more insight and understanding into the functionalization of CB, many more functionalized CB molecules have been synthesized and the research community has started to appreciate just how powerful functionalized CBs can be. While $\text{Me}_{12}\text{CB}[6]$ was first isolated and characterized in

2004^[22], its potential in molecular recognition was only recently discovered in 2021^[29]-which is 17 years after the isolation of Me₁₂CB[6]. In addition to presenting a summary of supramolecular applications of functionalized CBs, numerous potential strategies for functionalizing CBs was also covered. For instance, C-H activation is a powerful approach in C-C bond construction as it can accommodate a wide range of compounds and does not require an active functional group to proceed. There is a lot of research on C-H activation within the synthetic chemistry community. It is only a matter of time before researchers try to functionalize CB using C-H activation techniques; perhaps decades later, such a strategy may become a common method to functionalize CB derivatives. However, there are several challenges that must be addressed before C-H activation can be applied in the functionalization of CB. Firstly, the majority of experiments on C-H activation are carried out in organic solvents, it is difficult to carry out C-H activation if CBs cannot be dissolved in organic solvents. Therefore, the development of water-based C-H activation chemistries is needed or methods to enhance the solubility of unfunctionalized CBs in organic solvents. Secondly, although there are reports on oxidative coupling of C-H bonds adjacent to nitrogen atoms^[38], and two carbon atoms fulfil this criteria on each glycoluril subunit, there are no reports indicating oxidative coupling reactions can proceed if the nitrogen atom exists withing a urea functional group. This highlights that a lot of work needs to be done before functionalization of CBs using C-H activation becomes reality.

Functionalized CBs have shown their potential in many fields such as biosensors, platforms for drug delivery, and in a wide range of molecular recognition applications. Many potential applications, however, remain unknown such as attaching CBs onto the surface of proteins. There are still many problems waiting to be resolved, including low yields in the functionalization of larger CB homologues (CB[7,8]) and the isolation and potential functionalization of larger CB homologues, such as CB[9], which has not yet been achieved. Nevertheless, with a clear trend of increased research activities in CB and related fields, these problems will eventually be solved leading to exciting new possibilities.

References

- [1] Fyfe, Matthew; Stoddart. "Synthetic supramolecular chemistry." *Acc. Chem. Res* 30 (1997): 393-401.
- [2] Huang., et al. "Pillararenes, a new class of macrocycles for supramolecular chemistry." *Acc. Chem. Res.* 45 (2012): 1294-1308.
- [3] Krzysztof Szalewicz. "Hydrogen Bond" *Encyclopedia of Physical Science and Technology (Third Edition)*, 2003, Pages 505-538
- [4] Deng, et al. " π - π stacking interactions: Non-negligible forces for stabilizing porous supramolecular frameworks." *Sci. Adv.* 6.2 (2020): eaax9976.
- [5] 董运红, 曹利平. "Functionalization of Cucurbit [n] uril." *Prog. Chem.* 28.7 (2016): 1039-1053.
- [6] Issacs, Briken, et al. "Toxicology and drug delivery by cucurbit [n] uril type molecular containers." *PLoS One* 5.5 (2010): e10514.
- [7] Scherman, et al. "Cucurbituril-based molecular recognition." *Chem. Rev.* 115.22 (2015): 12320-12406.
- [8] Behrend, Robert; Meyer, Rusche. "I. Ueber condensationsproducte aus glycoluril und formaldehyd." *Justus Leibigs Ann. Chem.* 339.1 (1905): 1-37.
- [9] Freeman, W. A.; Mock, Shih. "Cucurbituril." *J. Am. Chem. Soc.* 103.24 (1981): 7367-7368.
- [10] Freeman, Mock; Shih. "Host-guest binding capacity of cucurbituril." *J. Org. Chem.* 48 (1983): 3618-3619.
- [11] Buschmann, Cleve; Schollmeyer. "Cucurbituril as a ligand for the complexation of cations in aqueous solutions." *Inorg. Chim. Acta.* 193.1 (1992): 93-97.
- [12] Kim et al. "New cucurbituril homologues: syntheses, isolation, characterization, and X-ray crystal structures of cucurbit [n] uril (n= 5, 7, and 8)." *J. Am. Chem. Soc.* 122

- (2000): 540-541.
- [13] Flinn, et al. "Decamethylcucurbit [5] uril." *Angew. Chem. Int. Ed. Eng.* 31.11 (1992): 1475-1477.
- [14] Sasmal, Sinha; Keinan. "Facile purification of rare cucurbiturils by affinity chromatography." *Org. Lett.* 6.8 (2004): 1225-1228.
- [15] Germain, Letoffe; Merlin, Buschmann. "Thermal behaviour of hydrated and anhydrous Cucurbituril: A DSC, TG and calorimetric study in temperature range from 100 to 800 K." *Thermochim. Acta.* 315.2 (1998): 87-92.
- [16] Masson et al. "Cucurbituril chemistry: a tale of supramolecular success." *Rsc Advances* 2.4 (2012): 1213-1247.
- [17] Kim, et al. "Novel molecular drug carrier: encapsulation of oxaliplatin in cucurbit [7] uril and its effects on stability and reactivity of the drug." *Org. Biomol. Chem.* 3.11 (2005): 2122-2125.
- [18] Yuan, Qi, et al. "Functionalization of cyclodextrins via reactions of 2, 3-anhydrocyclodextrins." *J. Org. Chem.* 68.24 (2003): 9456-9466.
- [19] Reinhoudt, et al. "Selective functionalization and flexible coupling of cyclodextrins at the secondary hydroxyl face." *J. Org. Chem.* 60.20 (1995): 6537-6545.
- [20] ZHAO. *Functionalized cucurbituril derivatives as supramolecular building blocks*. Diss. The University of New South Wales, 2017.
- [21] Stoddart, et al. "Decamethylcucurbit [5] uril." *Angew. Chem. Int. Ed. Eng.* 31.11 (1992): 1475-1477.
- [22] Sasmal, Sinha; Keinan. "Facile purification of rare cucurbiturils by affinity chromatography." *Org. Lett.* 6.8 (2004): 1225-1228.
- [23] Tao, et al. "Synthesis of partially methyl substituted cucurbit [n] urils with 3a-methyl-glycoluril." *J. Mol. Struct.* 875.1-3 (2008): 442-446.
- [24] Kim, et al. "Cucurbit [n] uril derivatives soluble in water and organic solvents." *Angew. Chem.* 113.22 (2001): 4363-4365.
- [25] Wang et al. "A cucurbit [5] uril analogue from dimethylpropanediurea-formaldehyde condensation." *Chem. Commun.* 51.14 (2015): 2890-2892.
- [26] Isobe, Sato; Nakamura. "Synthesis of disubstituted cucurbit [6] uril and its rotaxane

- derivative.” *Org. Lett.* 4.8 (2002): 1287-1289.
- [27] Xue, et al. “Synthesis of a symmetrical tetrasubstituted cucurbit [6] uril and its host-guest inclusion complex with 2, 2'-bipyridine.” *Chin. Sci. Bull.* 49.11 (2004): 1111-1116.
- [28] Issacs, et al. “Synthesis and self-assembly processes of monofunctionalized cucurbit [7] uril.” *J. Am. Chem. Soc.* 134.31 (2012): 13133-13140.
- [29] Tao et al. “Controllable Synthesis of Dodecamethylcucurbit [6] uril and Its Application in Separating Phenylenediamine Isomers.” *Cryst. Growth Des.* 21.5 (2021): 2993-2999.
- [30] Kim et al. “Facile synthesis of cucurbit [n] uril derivatives via direct functionalization: expanding utilization of cucurbit [n] uril.” *J. Am. Chem. Soc.* 125.34 (2003): 10186-10187.
- [31] Zhao, Lloyd; Scherman. “Monofunctionalised cucurbit [6] uril synthesis using imidazolium host-guest complexation.” *Chem. Commun.* 48. (2012): 3070-3072.
- [32] Kaifer et al. “Synthesis and binding properties of monohydroxycucurbit [7] uril: a key derivative for the functionalization of cucurbituril hosts.” *J. Org. Chem.* 83.10 (2018): 5467-5473.
- [33] Bardelang, Ouari et al. “Comprehensive synthesis of monohydroxy-cucurbit [n] urils (n= 5, 6, 7, 8): high purity and high conversions.” *J. Am. Chem. Soc.* 137.32 (2015): 10238-10245.
- [34] Bardelang, Ouari et al. “Correction to “Comprehensive synthesis of monohydroxy-cucurbit [n] urils (n= 5, 6, 7, 8): high purity and high conversions.”” *J. Am. Chem. Soc.* 138.6 (2016): 2060.
- [35] Briken, Issacs, et al. “Cucurbit [7] uril containers for targeted delivery of oxaliplatin to cancer cells.” *Angew. Chem. Int. Ed. Eng.* 52.46 (2013): 12033-12037.
- [36] Wemmer, et al. “Directly functionalized cucurbit [7] uril as a biosensor for the selective detection of protein interactions by ¹²⁹Xe HyperCEST NMR.” *Chem.--Eur.J.* 25.24 (2019): 6108-6112.
- [37] Park, et al. “3D tissue engineered supramolecular hydrogels for controlled chondrogenesis of human mesenchymal stem cells.” *Biomacromolecules* 15.3 (2014):

707-714.

[38] Yoo, Li. "Cross-dehydrogenative coupling reactions of sp³-hybridized C–H bonds." *CH Activation* (2009): 281-302.