Exploration of Bioactive Compounds of Ginger as a Folk Remedy for Migraines

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EXPLORATION OF BIOACTIVE COMPOUNDS OF GINGER AS A FOLK REMEDY FOR MIGRAINES

by

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ABSTRACT

Ginger (*Zingiber Officinale*) has been used in Asia for centuries to treat various ailments. Ginger has been reported to alleviate migraine pain via four bioactive compounds that can reduce nitric oxide synthase (NOS) resulting in the inhibition of nitric oxide (NO). The inhibition of nitric oxide results in the vasoconstriction of the intracranial blood vessels alleviating migraine pain. It is hypothesized that ginger has structural similarities to vasoconstrictor drugs causing similar receptor interactions. A review of the bioactive compounds in ginger and popular vasoconstrictor drugs was done to determine structural similarities. The results of this study show that the compounds in ginger share no structural similarities with vasoconstrictor drugs used in the treatment of migraine headaches.

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CHAPTER ONE: INTRODUCTION

A migraine is characterized as a moderate to severe throbbing pain with symptoms of nausea, vomiting, sensitivity to light (photophobia), sound (phonophobia) and head movements.[1] Migraines affect 12% of the population and result in decreased work productivity and performance. In 2004, the Headache Classification Committee of International Headache Society (IHS) published a paper with a new classification of migraines called 'migraines with aura.' The original migraine definition was kept the same, however 'migraine with aura' was used to define a migraine in which reversible loss of vision, speech, and sensory occur.[2]

Migraines arise by activation of serotonin receptors leading to the release of NO (nitric oxide) resulting in vasodilation. NO can further induce vasodilation by the release of neurotransmitters such as calcitonin gene-related peptide (CGRP) and substance P. Ginger can alleviate migraine pain due to its ability to inhibit NO resulting in vasoconstriction. [15-16] These findings suggest that ginger may have structural similarities to vasoconstrictor drugs. This study seeks to determine whether the compounds in ginger share structural similarities to vasoconstrictor drugs.

CHAPTER TWO: LITERATURE REVIEW

2.1 Migraine History

In 1938, Harold Wolff established the first migraine theory known as the vascular theory. Wolff found that patients with migraines had extracranial vasodilation that could be treated by using vasoconstrictors. Wolff concluded that vasodilation results in migraine pain and vasoconstriction could be used to alleviate the pain.[3] After this finding, DeVries suggested that vascular pulsation leads to activation of stretch receptors causing the release of neuropeptides such as calcitonin gene-related peptide (CGRP) from perivascular nerves. CGRP is a potent vasodilator, which can lead to migraine pain.[4] Although the vascular theory was initially believed to be the only mechanism of action by which migraines arise, another theory was created which further expands on the pathology of a migraine.

In 1983, James W. Lance showed that the blood flow changes in migraines could be created by stimulation of the brain stem leading to the formation of the neurogenic theory.[5] In 1993, Moskowitz further supported this argument by publishing a study on the inflammation of the dural membrane. Moskowitz noticed that the release of vasopeptides from the trigeminal axons of the dura (outer layer of the meninges which is the membrane covering brain and spinal cord) and pia (inner layer of the meninges) mater produced an inflammatory reaction with pain.[6] This inflammatory response stimulates the trigeminal ganglion causing protein extravasation (protein leakage). The proteins released are

vasoactive peptides such as calcitonin gene-related peptides (CGRP) and substance P.[7] These two vasoactive peptides play vital roles in dural inflammation because substance P causes protein extravasation (protein leakage). CGRP works synergistically with substance P by increasing blood flow in the dura and inhibiting metabolism of substance P resulting in dural inflammation and nerving ending irritation.[8] Based on these findings the neurogenic theory demonstrated that vascular changes result in inflammation and vasodilation of dural membrane causing a migraine.

Two major theories were established that explained the mechanism of migraines, however, these did not account for 'migraine with aura'. This phenomenon was addressed in the neurological theory, which states that 'migraine with aura' is caused by depolarization of cortical neurons from the occipital lobe (back of the head) toward the frontal lobe.[9] Depolarization of the cortical neurons results in sensory or motor impairment leading to loss of vision, speech symptoms, and sensory symptoms.[10] This process is called cortical spreading depression (CSD). CSD is typically coupled with a period of hyperemia (increased blood volume) followed by a period of oligemia (decrease blood volume). Studies suggest that a catalyst of CSD is nitric oxide (NO), a potent vasodilator.[10]

Although not much is understood on migraines, these three theories (vascular, neurogenic, neurological) help to provide insight on the modes of action of migraine.

The following literature review will focus on the connection between migraines and ginger (vasoconstrictor).

2.2 Relationship between serotonergic receptors, nitric oxide, and calcitonin gene-related peptide in migraines

The 5-hydroxytryptamine (5-HT) receptor is a serotonin receptor that has been reported to control migraines via ligand-receptor interactions. [11] For example, a recent study has shown that when the 5-HT_{2A} receptor is activated it causes pain, inflammation, and vasodilation. Initial interest in this receptor occurred in an experiment where researchers noticed an increase in 5-HT_{2A} (ligand) on a platelet membrane of a migraine patient.[12] This observation had motivated scientists to determine the relationship between the 5-HT_{2A} receptor and the nitric oxide (NO) system. NO is an essential factor in the development of migraines due to its ability to cause vasodilation, which was shown in a study using nitroglycerin (NO donor) to induce migraines. [13]

In order to determine the relationship between nitric oxide and HT_{2A} receptor, two experiments were carried out. The first experiment determined the effects of 5-HT_{2A} receptor agonist 1,2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) on chemical (discomfort pain sensation) and thermal nociception (burning pain). While the second experiment conducted, investigated the effect of DOI on regional cerebral blood flow and NOS (nitric oxide synthase) expression in the trigeminovascular nerve fibers and neurons. These experiments were run on mice, which would be dissected, and immunohistochemically studied.

The results of these two experiments showed that the 5-HT receptor caused cerebral hyperemia (increased blood flow in the brain) and increased nitric oxide synthase (NOS) expression in trigeminal ganglion and trigeminal nucleus caudalia. Additionally, researchers found that the 5-HT_{2A} receptors activated by DOI caused activation of trigeminovascular NO pathway similarly to mice injected with nitroglycerin (NTG), a nitric oxide donor that causes migraines. DOI activates the NO pathway by increasing NOS cells in the trigeminal nerves. These findings lead to the conclusion that nitric oxide synthesis occurs by activation of the 5-HT_{2A} receptor. The 5-HT_{2A} receptor causes an increase in intracellular calcium resulting in activation of NOS pathway. NOS allows the release of NO from neurons. Once released, NO diffuses back into the presynaptic terminal to release neurotransmitters such as substance P and CGRP.[14] These findings suggest a link between NO and CGRP, which is supported by two studies that demonstrated NO-donor-triggered migraines cause an increase of CGRP even when blocked by sumatriptan.[15, 16]

The 5-HT_{2A} receptor can also be down regulated via drugs result in the alleviation of migraines. Furthermore, the 5-HT_{2A} receptor is not the only type of serotonin receptor that can alleviate migraines. The genes in our body code for different types of serotonin receptors each with a unique mechanism of action and effect on migraines, which can be seen in Table 1. Some receptors have subclasses with the same result but are just encoded by different genes. For example, HTR_{1A} gene encodes the HT_{1A} receptor, while HTR_{1B} gene encodes the HT_{1B} receptor.[17-19]

Table 1: Classification of Serotonin Receptor**s**

Receptor	**Subclasses**	**Ligand Type**	**Mechanism of action**	**Effect**
5-HT$_1$	5-HT$_{1A, B, D, E, F}$	Agonist	Allows the decrease of cyclic adenosine monophosphate (cAMP)	Induces vasoconstriction and reduces inflammation by inhibition of substance (CGRP, substance P, NO) from trigeminal nerve causing redistribution of blood flow resulting in alleviation of migraine pain.
5-HT$_2$	5-HT$_{2A, B, C}$	Antagonist	Allows the increase levels of IP3 and DAG	Prevents increase of intracellular calcium resulting decrease of nitric oxide causing vasoconstriction causing alleviation of migraine pain
5-HT$_3$	N/A	Antagonist	Prevents depolarization of the plasma membrane	Reduce vascular pain caused by inflammation and inhibition of substance (CGRP and substance P from the trigeminal nerve.
5-HT$_4$	N/A	Agonist	Allows increase of cyclic adenosine monophosphate (cAMP)	Intracranial vasoconstriction

5-HT$_7$	N/A	Antagonist	Allow increase of cyclic adenosine monophosphate (cAMP)	Decreases level of CGRP and substance p resulting in vasoconstriction relieving migraine pain

2.3 Components of Ginger

Table 2: Species of Ginger

Species of Medicinal Ginger	**Origin**
Jamaican Ginger	Jamaica
Zingiber Officinale Roscoe	Western nations (USA)
Shokoyo **(dried rhizome of Z. Officinale var. rubens)**	Japan
Kankyo **(steamed and dried rhizome of Z. officinale var rubens)**	Japan
Red ginger **(rhizome of Z. officinale var. rubra)**	Indonesia
White ginger **(rhizome of Z. officinale var amarum)**	Indonesia

Ginger is a member of the plant family Zingiberaceae and can be found in many different species as shown in Table 2.[20-21] However, the species that has been studied is *Zingiber Officinale Roscoe*. Ginger has been shown to have at least 115 constituents in fresh and dried ginger. It is important to note that the individual components in ginger depend on the origin, processor, and whether it is fresh, dried, or processed.[22] Methanolic extractions have been used to isolate 31 compounds in fresh ginger.[23] Of these isolated compounds, 14 bioactive compounds have been found. These bioactive compounds are [4]-gingerol, [6]-

gingerol, [8]-gingerol, [10]-gingerol, [6]-paradol, [14]-shogaol, [6]-shogaol, 1-dehydro-[10]-gingerdione, [10]-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A, 1,7-bis-(4′ hydroxyl-3′ methoxyphenyl)-5-methoxyhepthan-3-one, and methoxy-[10]-gingerol.[24] However in regards to migraines the following bioactive compounds shown below have been noted to act as potent antioxidants.[25]

Figure 1: Structure of [6]-Gingerol

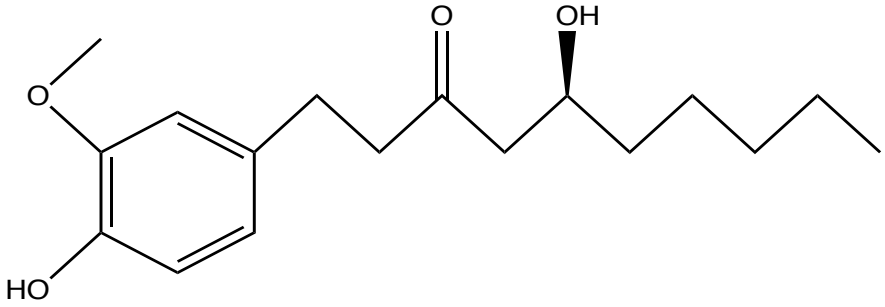


Figure 2: Structure of [6]-Shogaol

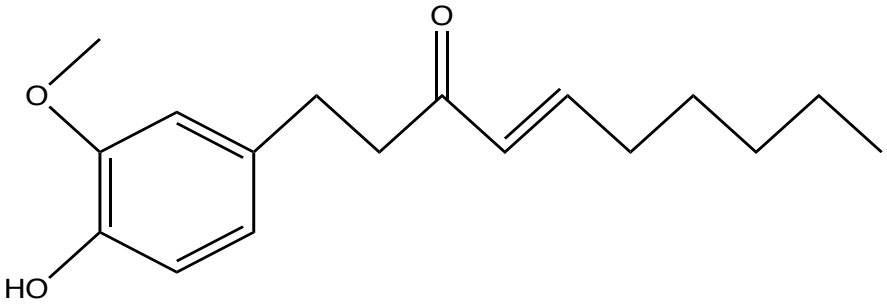


Figure 3: Structure [1]-Dehydro-[10]-gingerdione

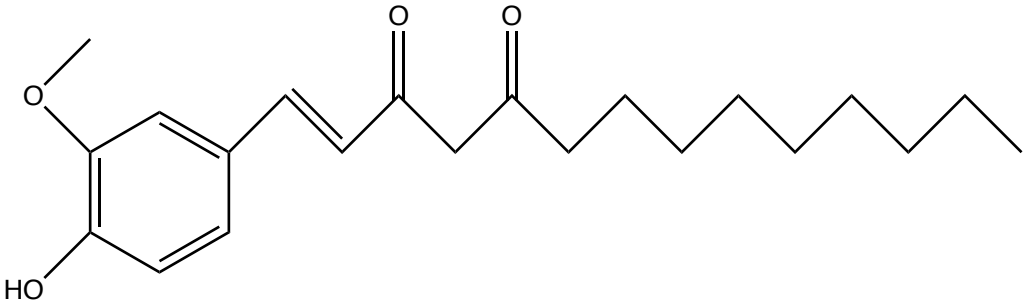
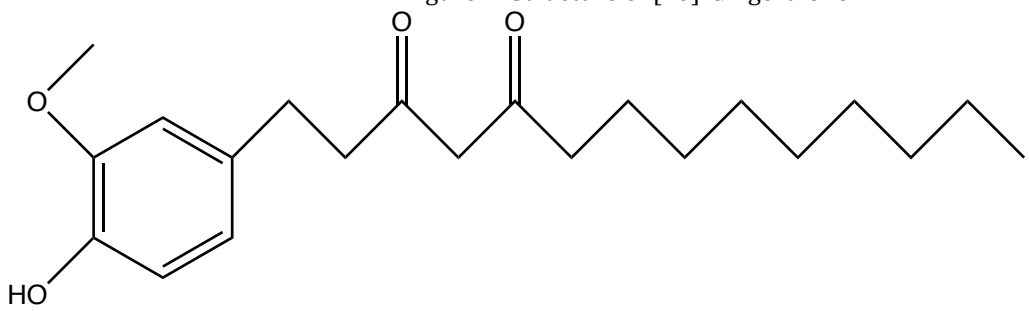


Figure 4: Structure of [10]-Gingerdione



2.4 Relationship of Ginger & Migraines

The Chinese and Indians have used Ginger for over 400 years to treat colds, arthritis, nausea, hypertension, and migraines. Treatment of these ailments is due to the antioxidant, anti-inflammatory, anti-nausea, and anti-carcinogenic properties of ginger.[25] However, to verify that ginger treats migraines a few studies have been done. For example, a study by Maghbooli compared the efficacy of ginger and sumatriptan (potent vasoconstrictor used to treat migraines) in a group of 100 men and women with acute migraine pain. The patients were given 250 mg of dried ginger powder or 50 mg sumatriptan. The participants recorded the time the headache began, headache severity before taking the capsule, and degree of pain relief afterward. The results showed that ginger was equally affective in relieving headaches while demonstrating minor digestive symptoms.[26]

Another study that demonstrated the effectiveness of ginger against migraines was a double-blind placebo control pilot study of sublingual feverfew and ginger. In this study, patients that met the international criteria of migraines were given sublingual feverfew/ginger capsule or a placebo. The results showed that 63% of patients receiving

sublingual feverfew/ginger capsule found pain relief. This study showed that the sublingual ginger/feverfew is safe and should be used as the first line of defense for migraines.[27]

In addition to these studies, Ippoushi has demonstrated ginger's ability to inhibit NO.[28] However, before looking into this mechanism, a brief explanation of immunology is needed to understand the experiment. In our primary line of defense, macrophages detect pathogens resulting in the recruitment of other cells to the pathogen (inflammation) or destruction of the pathogen. Macrophages have pathogen recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS). These macrophages will then bind to the pathogen and engulf them via phagocytosis. This results in the formation of a phagolysosome with in the macrophage. The macrophage can then release radical oxygen species with in the phagolysosome such as nitric oxide to kill the pathogen. [29]

Ippoushi created a study, in which he could stimulate the production of nitric oxide by injecting mice with LPS. In this study, Ippoushi found that in the LPS-stimulated macrophage, [6]-gingerol inhibited NO production and reduced inducible nitric oxide synthase (iNOS), which is stimulated in response to stress.[28] Ippoushi's work was later complemented by a researcher named Koh, who showed that [6]-shogaol, 1-dehydro-[10]-gingerdione, and [10]-gingerdione decreased LPS-induced NO production, and reduced iNOS expression.[30] This study shows that the bioactive compound in ginger can inhibit NO

production, which results in vasoconstriction. This experiment is supported by the structural properties of the bioactive compounds shown above. The bioactive compounds of ginger are phenolic compounds, which can act as nitric oxide production inhibitors.[31]

Ginger has also shown the ability to partially activate 5-HT_{1A}, which induces vasoconstriction and reduces inflammation by inhibition of substances (CGRP, Substance P, NO) from trigeminal nerve causing redistribution of blood flow resulting in alleviation of migraine pain.[32] Based on this information it can be concluded that the bioactive compounds in ginger play a critical role in the inhibition of NO, which in turn play a role in the alleviation of migraines.

2.5 Hypothesis and Intent

The studies on the bioactive compounds of ginger suggest possible structural similarities to vasoconstrictor drugs used to treat migraines. Therefore, a comprehensive review is done to determine structural similarities.

CHAPTER 3: METHODOLOGY

3.1 Experimental approach

Our approach from the beginning of this experiment was to do a comprehensive review on the mechanism of migraines. From this literature review, we learned about the role of 5-HT receptors, nitric oxide, calcitonin-gene related peptide, and substance P in migraine headaches[15, 16,17,18]. After establishing a background in migraines, the next goal of this project was to compile a list of references that discussed ginger as a treatment for migraine headaches. Once this list was collected, extensive research was done to determine whether these papers had scientific validity. After the scientific validity of ginger's role in a migraine was determined, it was essential to find the connection between the mechanism of ginger and migraines. Once the relationship between migraines and ginger was established, the final piece of the project required a compiled list of popular vasoconstrictor drugs and their mechanism of action against migraines. These drugs were then compared with bioactive compounds in ginger to determine any structural similarities.

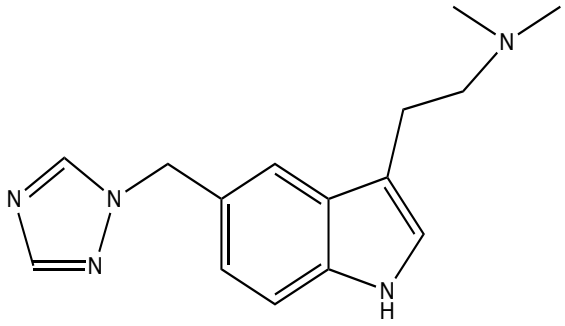
CHAPTER 4: RESEARCH FINDINGS

Review of vasoconstrictor drugs and mechanism of action against migraines

4.1 Triptan Family

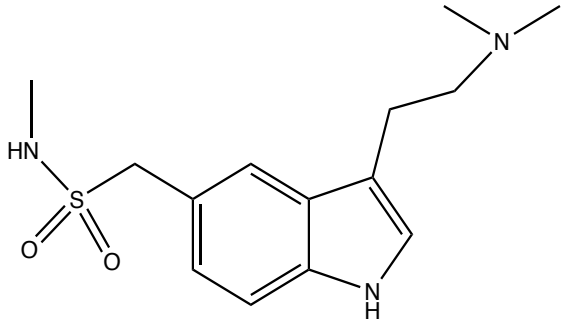
The triptan family is a class of highly selective 5-HT receptor agonists whose actions can relieve migraines through vasoconstriction of intracranial blood vessels, inhibition of vasoactive neuropeptide release (CGRP), and blocking of pain signals. The onset action of these drugs typically ranges from 30 to 60 minutes. The most common triptan drugs used to treat migraines are Rizatriptan, Sumatriptan, Eletriptan, and Almotriptan, which can be seen in the figures below.[33]

Figure 5: Structure of Rizatriptan



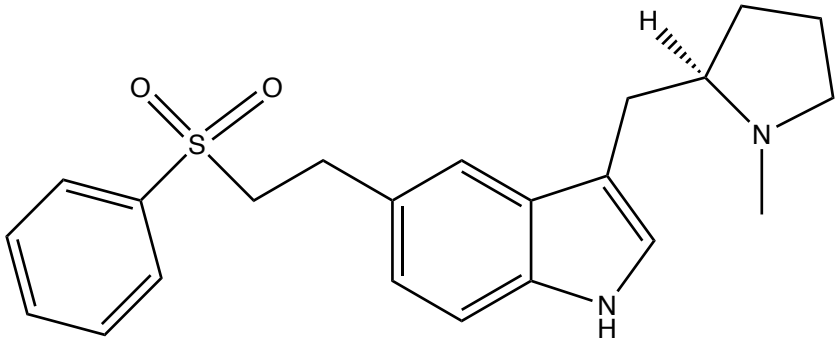
Rizatriptan (Maxalt) is a 5-$HT_{1B, 1D}$ receptor agonist, which induces vasoconstriction by inhibiting release of CGRP from trigeminal nerve.[33]

Figure 6: Structure of Sumatriptan



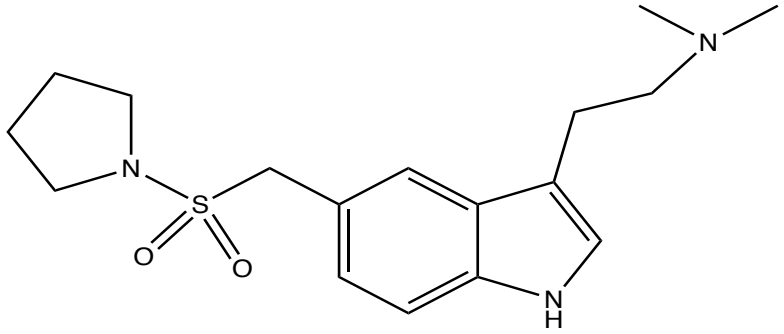
Sumatriptan (Imitrex) is a 5-$HT_{1B, 1D}$ receptor agonist that causes vasoconstriction of dilated arteries and decreases activity of the trigeminal nerve.[33]

Figure 7: Structure of Eletriptan



Eletriptan (Relpax) binds to the 5-$HT_{1B, 1D, 1F}$ receptor with high affinity and blocks the release of substances from nerve endings and is believed to reduce swelling of blood vessels around the brain.[33]

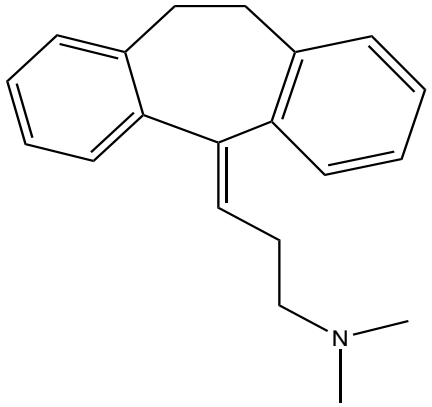
Figure 8: Structure of Almotriptan



Almotriptan binds to the 5-$HT_{1B, 1D}$ receptor with high affinity and leads to vasoconstriction of cranial blood flow, which causes redistribution of blood flow.[33]

4.2 Elavil (Amitriptyline)

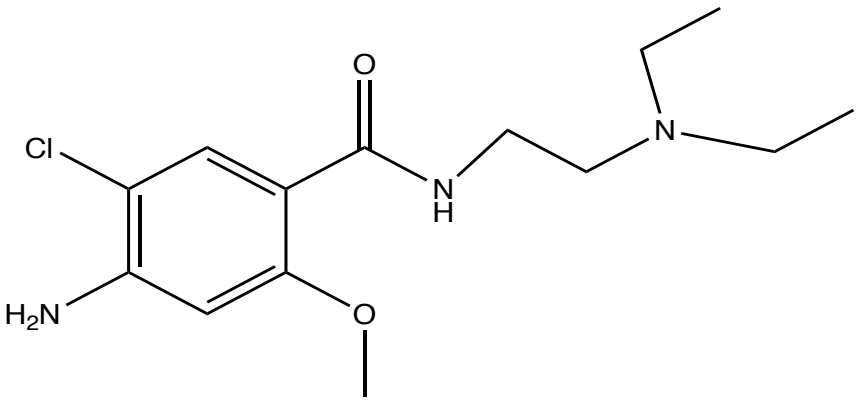
Figure 9: Structure of Elavil



Elavil (Amitriptyline) is a tricyclic antidepressant (TCA) that has been reported to be efficient in the treatment of migraines.[33] Elavil is a 5-HT_2, $5HT_3$, and 5-HT_7 receptor antagonist that causes vasoconstriction, reduction of CGRP release, and prevents inflammatory vascular pain.[34-35]

4.3 Metoclopramide

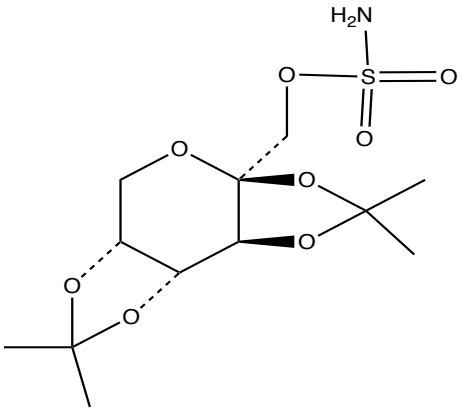
Figure 10: Structure of Metoclopramide



Metoclopramide is a popular drug used to treat migraines due to its ability to act as a 5-HT_3 receptor antagonist and 5-HT_4 receptor agonist. Metoclopramide's ability to act as a 5-HT_3 antagonist causes alleviation of pain by reduction of inflammation and inhibition of the trigeminal nerve (decrease in substance P). While activation of the 5-HT_4 receptors has been reported to cause intracranial vasoconstriction.[36-37]

4.4 Topiramate

Figure 11: Structure of Topiramate

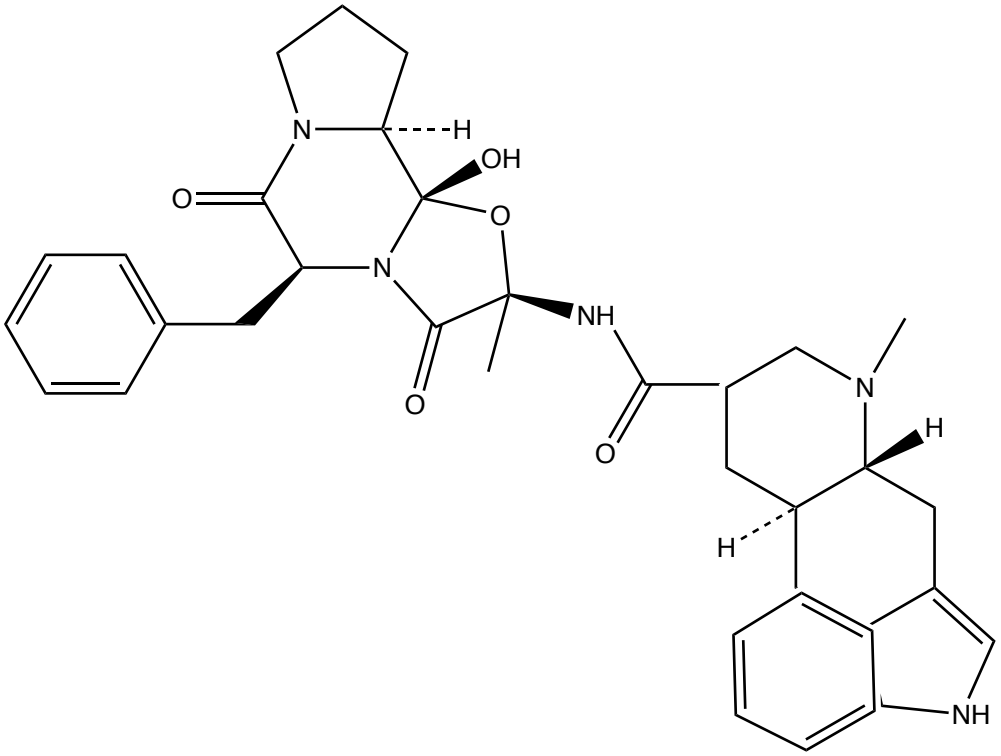


Topiramate is a fructose 1,6- diphosphate analog that blocks voltage-activated Na^+, Ca^{2+}, and regulates K^+ channel. Inhibition of Na^+ and Ca^{2+} voltage-gates reduces the sensitivity of

trigeminal nerve, which in turn reduces the release of neurotransmitters (substance P, NO, CGRP) that result in nociception (pain).[38]

4.5 Dihydroergotamine

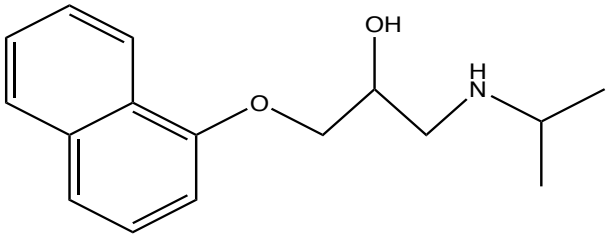
Figure 12: Structure of Dihydroergotamine



Dihydroergotamine is an ergot alkaloid (nitrogenous fungal metabolites), which stimulates the 5-HT_1 receptor on the trigeminal nerve terminals blocking the release of neuropeptides (CGRP, substance P) which plays a role in migraine pain. DHE also demonstrates the ability to inhibit trigeminal pain in the brainstem and neurogenic inflammation in trigeminovascular system.[33, 39]

4.6 Propranolol

Figure 13: Structure of Propranolol



Propranolol is a beta-1 blocker that prevents migraine activity by reducing the neuronal firing rate of noradrenergic neurons. Propranolol is also a 5-$HT2_{B,C}$ receptor antagonists that causes cranial vasoconstriction and increased cranial capillary permeability. [40]

4.7 Chemical Structure Analysis of Vasoconstrictor Drugs and Ginger

At the beginning of this project, a literature review was done to understand the role of compounds in ginger against migraines. The literature findings demonstrated that ginger acts as a vasoconstrictor, which relieves migraines. These discoveries led to the hypothesis that the compounds in ginger must have structural similarities to popular vasoconstrictor drugs. However, based on the findings shown in Table 3, it can be seen that the bioactive compounds in ginger share no structural similarities to the vasoconstrictor drugs used to treat migraines.

Table 3: Structural Analysis of Vasoconstrictor Drugs and Ginger

Compound	**Structural Analysis**
Ginger	**Main Structural Components**
[6]-Gingerol	• **Decan-3-one** • **4-Hydroxy-3-methoxyphenyl** • **5-Hydroxy**
[6]-Shogaol	• **Dec-4-en-3-one**

	• **4-Hydroxy-3-methoxyphenyl**
[1]-Dehydro-[10]-gingerdione	• **Tetradec-1-ene-3,5-dione** • **4-Hydroxy-3-methoxyphenyl**
[10]-Gingerdione	• **Tetradecan-3,5-dione** • **4-Hydroxy-3-methoxyphenyl**
Vasoconstrictor Drugs	
Rizatriptan	• **1,2,4- Triazole** • **Indole** • **N,N-dimethylethanamine**
Sumatriptan	• **N-methyl sulfonamidomethyl** • **Indole** • **N,N- dimethylethanamine**
Eletriptan	• **2-(Benzenesulfonyl)ethyl** • **Indole** • **N-methylpyrrolidin**
Almotriptan	• **Pyrrolidin** • **Indole** • **Sulfonylmethyl** • **N,N-dimethylethamine**
Elavil	• **Dibenzocycloheptene** • **N,N-dimethylpropan-1-amine**
Metoclopramide	• **2-Methoxybendamize** • **N,N-diethylethaneamine**
Topiramate	• **Methylsulfamate** • **Pinacol** • **Tetrahydropyran**
Dihydroergotamine	• **Indole** • **Phenyl**
Propranolol	• **Naphthalene** • **Isopropylamine**

CHAPTER 5: DISCUSSION OF RESULTS AND CONCLUSION

5.1 Discussion

The origin and mechanism of migraines are not fully understood; Current research suggests that a migraine is caused by vasodilation (via activation of 5-HT receptors). Activation of 5-HT receptor results in cerebral hyperemia (increased blood flow to the brain) and increased nitric oxide synthase (NOS) expression in trigeminal ganglion and trigeminal nucleus caudalia.[14] NOS allows the release of NO (potent vasodilator) from neurons. Once released, NO diffuses back into the presynaptic terminal to release neurotransmitters such as substance P (pain) and CGRP (potent vasodilator). [15, 16] NO has also been shown to cause depolarization of cortical neurons from the occipital lobe (back of the head) toward the frontal lobe.[9] Depolarization of the cortical neurons results in sensory or motor impairment (loss of vision, speech, and senses).[10] To relieve the pain and symptoms, patients are treated with vasoconstrictor drugs as shown in Table 3.

The bioactive compounds in ginger are also not fully understood, but many studies have shown that ginger can alleviate migraine pain by the reduction of NOS expression resulting in the inhibition of NO. Ginger has also been reported to act as a partial HT_{1A} agonist, which induces vasoconstriction and reduces inflammation by inhibition of substances (CGRP, Substance P, NO) from trigeminal nerve causing redistribution of blood flow resulting in alleviation of migraine pain.[32]

Ginger's ability to act as a vasoconstrictor has led to the hypothesis that the bioactive compounds in ginger must have structural similarities to popular vasoconstrictor drugs. Through further research, this study has shown that the bioactive compounds in ginger share no structural similarities with vasoconstrictor drugs used to treat migraines as shown in Table 3.

5. 2 Conclusions and Future Work

Most research studies suggest that migraines are caused by vasodilation, which is not always the case. A migraine can result from genetic and environmental factors, which play a role in the severity of the condition. Further research should be done to gain a better understanding of the mechanisms of migraines. Additionally, researchers should continue to investigate the bioactive compound in ginger, because only 31 out of 108 compounds in ginger have been identified and 14 bioactive compounds have been found, which indicates that the unknown compounds may help clarify the mechanism of ginger against migraines.

Moreover, future researchers should consider comparing the effects of vasoconstrictor drugs and ginger on cerebral arteries. The findings of these experiments may help to explain ginger's ability to alleviate migraine pain.

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