THE EFFECTS OF NEGRO PEPPER EXTRACT ON PROSTAGLANDIN LEVEL DURING THE GESTATION PERIOD OF WISTAR RAT

BY

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DEDICATION

I dedicate this work to God Almighty, my family and friends.

ACKNOWLEDGEMENT

I want acknowledge God Almighty who is the provider of knowledge, wisdom and understanding. I also want to appreciate my parents and siblings who support me during my undergraduate journey. I also acknowledge my supervisor.

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ABSTRACT

Excessive prostaglandin production had been reported to lead to uterine contraction and premature cervical changes contributing to preterm birth. The aim of this study is to determine the effect of negro pepper on the prostaglandin level during the gestation period of wistar rat. Sixteen (16) female wistar rats weighing 140 to 160 were purchased from the animal house of the Department of Anatomy, University of Benin. The rats were acclimatized for two weeks to the laboratory condition with free access to food and water. The dry fruits after being grind were soaked with n-hexane using maceration method for 24 hrs and were filtered to obtain the filtrate which was evapourated to obtain the oil. The female rats were mated with male rate in the ratio of 2:1. The rats were grouped into 4 groups (A, B, C, D) in two phases (Germinal and Embryonic Phase) and administered negro pepper extract orally at the doses of 0.25ml/Kg, 0.5ml/Kg and 1ml/Kg respectively daily for 7 days.

The rats were sacrificed using chloroforms anesthesia, the uterus was collect from the animal and homogenated with buffer solution and then centrifuged to collect the Supernatant which was used for the biochemical analysis. The result were statistically analyzed, results obtained were expressed as mean ±SEM (Standard Error of Mean). Differences among the means were determined by one way analysis of variance (ANOVA). Values were considered statistically significant if P value is less than 0.05 ($P<0.05$). Results: there was a significant increase in PGE_2 level at 0.5ml/kg compared with control, though there was no significant differences in PGE_2 at 0.25ml/kg compared with control in the embryonic phase and there was a significant decrease in PGE_2 at 0.25ml/kg and 0.5ml/g in the Germinal phase compared with control though there was no significant difference in 1.0ml/kg compared to control. In conclusion, Negro Pepper Extract at 0.5ml/kg significantly increased PGE_2 level at the embryonic phase but significantly decreased PGE_2 in 0.25ml/kg and 0.5ml/kg in the germinal phase compared to control showing that administration of negro pepper extract during pregnancy maybe detrimental to the pregnancy.

CHAPTER ONE

INTRODUCTION

Xylopia aethiopica commonly known as Negro pepper, is a tropical evergreen fruit with seeds that are aromatic and contain bitter principles. *Xylopia aethiopica* belong to the Annonaceae family (Obiri *et al*., 2014) naturally grow in the Savanna region of Africa, particularly in Ghana, Nigeria, Cameroon, Ethiopia, and Senegal to name a few (Yin *et al*., 2019) with its essential oil reported to contain substances such as β-pinene- a monoterpene hydrocarbon, bisabolene- a sesquiterpene hydrocarbon, terpinene-4-ol which is an alcohol and the oxide 1, 8-cineole among others (Fetse *et al*., 2016). Negro pepper is used as mouth wash to relieve tooth ache, rheumatism, arthritis and for preparing post partum tonic (Llusanya *et al.*, 2012).

Prostaglandins are group of physiologically active lipid compound called eicosanoids (Ricciotti and Fitz Gerald, 2011) having diverse hormone-like effect in animals. They are derived enzymatically from fatty acid (arachidonic acid) by the enzyme cyclooxygenase (COX), also known as prostaglandin endoperoxide synthase (PTGS) (Vane *et al*., 1995). COX exist in two isoforms; COX1 (which play a role in protecting stomach lining and maintaining normal cellular processes) and COX2 (is an inducible enzyme which is rapidly up regulated in response to

inflammation, injury and other stimuli). Prostaglandin is classify into two; vasoconstrictive prostaglandin(prostaglandin $F_2\alpha$) and vasodilatory prostaglandins(prostaglandin I_2, prostaglandin E_1 and prostaglandin E_2) (Fitz Gerald *et al.,* 2001). Prostaglandins are present in maternal blood, urine, and amniotic fluid during pregnancy (Schlembach *et al*., 2009).

During a normal pregnancy, prostaglandin level undergoes dynamic changes to support the maintenance and progression of pregnancy. In the early stage of pregnancy, prostaglandin levels are relatively low, contributing to the stability of the pregnancy and preventing of premature labor. As pregnancy advances and approaches full term, the concentration of prostaglandin particularly prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α) gradually increase. (Niringiyumukiza *et al.*, 2018). In preterm labor, there is excessive prostaglandin production which lead to uterine contractions and premature cervical changes contributing to preterm birth. (Thomas *et al,.*2014).

Hart *et al,* (2000) reported that terpinene-4-ol contained in tea tree oil reduce the production of tumor necrosis factor alpha(TNFalpha), interleukin (IL) -1 beta, interleukin 8, interleukin 10 and prostaglandin E2 (PGE2) in an invitro study.

Kim *et al,* (2013) reported that sabinene contained in Hallabong oil were found to inhibit nitric oxide and prostaglandin E2 production in an in vivo study.

Furtado *et al,* (2024) reported that kaurenol (Kaur-16-ol) contain in copaiba oil were found to cause the release of nitric oxide, serotonin and prostaglandin.

Despite all these works, there is no literature review on prostaglandin level during pregnancy

1.1 Justification of study

Negro pepper has a wide range of documented uses and contains phytochemicals that are capable of affecting the level of prostaglandin concentration . Furtado *et al.,*(2024) reported that Kaur-16-ol present in Copaiba oil causes increase in prostaglandin level. In macrophage tissues in an invitro study. Hart *et al.,* 2000 reported that Terpinen-4-ol present in Tea tree oil causes decrease in prostaglandin level in activated human peripheral blood monocyte. However, the effect of negro pepper extract on prostaglandin level in pregnant wistar rat remains unknown

1.2 Aim of study

The aim of this study is to determine the effect of negro pepper on prostaglandin during gestation period of Wistar rat

1.3 Research Question

- Does the consumption of negro pepper affect the level of prostaglandin level during gestation period of Wistar rat?
- Is the effect dose dependent?
- What is the mechanism behind the effect of negro pepper on prostaglandin level during gestation period of Wistar rat?

1.4 Specific objectives of study

1. To determine if the consumption of negro pepper will affect the level of prostaglandin during the gestation period of Wistar rat.
2. To determine if it effect is dose dependent.
3. To determine the mechanism of this effect

CHAPTER TWO

LITERATURE REVIEW

2.1 XYLOPIA AETHIOPICA

2.1.1 Description of *Xylopia aethiopica*

Xylopia aethiopica (Uda) is a common herb found in South Eastern states of Nigeria that is used as a spice, stimulant, and flavouring agent (Okwunodulu *et al.*, 2023; Uzodike and Onuoha, 2010). Dietary nutritional contributions were justified by its approximate composition. 9.59% moisture, 6.97% ash, 13.89% protein, 9.28% fibre, 7.81% fat, and 52.94% carbohydrates were the approximate compositions reported by Zaragozá (2016). Because of its high fibre content, it helps with digestion, the body's absorption of water, bulky stool, and the avoidance of constipation. Higher fat content will also provide the energy and fatsoluble vitamins that nursing moms require. They are sources of protein that are required to replace deteriorated tissues. The carbohydrates included in *Xylopia aethiopica* make it a useful energy substrate. *Xylopia aethiopica* spices are widely employed in West African ethnomedicine because of their phytochemicals' protective effects and their associated antioxidant qualities, which go hand in hand with the vitamin and mineral's health advantages (Idris *et al.*, 2011).

The Annonaceae family plant *Xylopia aethiopica* is also referred to as Ethiopian or African guinea pepper. Both gramme positive and gramme negative bacteria are susceptible to its antimicrobial activities, and the phytochemicals in them have antioxidant qualities. In the conventional setups, these qualities are utilised in hot pepper soups (postpartum tonics) made for new mothers and nursing moms as an anti-infection and lactation aid. Additional applications include the treatment of cough, rheumatism, arthritis, stomach aches, and inflammations, as well as antipyretic (fever-reducing) properties (IIusaya *et al.*, 2012; Uzodike and Onuoha, 2010). According to Omodamiro *et al.* (2012), the seed extract helps postpartum women's uteruses contract. The antioxidant characteristics of medicinal plants are more desirable than those of manufactured substances, which can have harmful effects on health and have side effects (Omodamiro and Jimoh, 2014). Antioxidants work to counteract an overabundance of free radicals and shield cells from their harmful effects. By giving the free radical an electron to stabilise, they also aid in the prevention of disease (Omodamiro and Jimoh, 2014).

Dried *Xylopia aethiopica* fruit (Okwunodulu *et al.*, 2023)

2.1.2 Taxonomy of *Xylopia aethiopica*

Xylopia aethiopica, also known as the Negro pepper or African pepper, belongs to the Annonaceae family1. It is an evergreen, aromatic tree that can grow up to 20m high (Harvey-Brown, 2018). The plant's binomial name, aethiopica, refers to its origin in Ethiopia, although it is now most prominently grown as a crop in Ghana, Togo, and other parts of West Africa (Harvey-Brown, 2018). It is present in rain forests, especially near the coast, and also grows in riverine and fringing forest, and as a pioneer species in arid savanna regions (Harvey-Brown, 2018).

2.1.3 Uses of Xylopia aethiopica

Doors and partitions are made from the bark of the shrub. The wood is utilized in the construction of huts as joists, supports, scantlings, and roof ridges since it is known to be resistant to termite infestation. The wood is also used to make the spars, paddles, oars, and masts of boats. Wood was originally used in Togo and Gabon to create crossbows and bows for hunters and warriors (Johnson and Murray, 2018).

The plant's fruit or bark infusion has been used as a mouthwash to relieve toothaches and as a cure for bronchitis and dysenteric ailments. Additionally, it has been used as a medication to treat fever and biliousness. The bark is used to treat rheumatism, stomachaches, and asthma when steeped in palm wine (Johnson and Murray, 2018).

The fruit is used to flavour café Touba, a coffee beverage that is both the Mouride brotherhood's traditional drink and the nation's spiritual beverage in Senegal (Nmom *et al.*, 2020). The fruit was brought as a "pepper" to Europe during the Middle Ages. The fruit of the plant is a necessary component of regional soups made in the eastern region of Nigeria, which helps nursing young mothers. It is still a widely used spice for food and medicine seasoning in local trade throughout

Africa. Sometimes, the fruit is placed in water-filled jars to aid in purification (Johnson and Murray, 2018).

2.1.4 Ethnomedicinal Uses of *Xylopia aethiopica*

Xylopia aethiopica, commonly known as the African pepper or Guinea pepper, holds a significant place in traditional medicine due to its diverse range of health benefits. According to research conducted by Erhirhie and Moke in 2014, the plant has been traditionally employed in various medicinal contexts, with claims of efficacy as abortifacients, ecbolics, and treatment for ailments such as diarrhea, dysentery, stomach disorders, menstrual disorders, naso-pharyngeal infections, arthritis, rheumatism, and general infections.

In the realm of respiratory health, an infusion prepared from the bark or fruit of *Xylopia aethiopica* has been documented as a useful remedy for bronchitis.

Furthermore, the plant has been employed in addressing dysenteric conditions, showcasing its versatility in treating gastrointestinal issues. Beyond internal applications, the infusion has been recognized for its potential as a mouthwash, particularly in the context of alleviating toothaches (Erhirhie and Moke 2014),

The utilization of *Xylopia aethiopica* in traditional medicine is deeply rooted in cultural practices and has been passed down through generations. It reflects the profound knowledge of indigenous communities regarding the plant's medicinal

properties. While these traditional uses are fascinating, it is essential to note that further scientific research is needed to validate and understand the mechanisms behind the claimed health benefits of *Xylopia aethiopica* (Erhirhie and Moke 2014).

2.1.5 Ethnobiological Uses of *Xylopia aethiopica*

In addition to its extensive applications in traditional medicine, *Xylopia aethiopica* serves practical purposes in the realm of construction and craftsmanship. According to the findings by Erhirhie and Moke in 2014, the plant's bark and wood have been harnessed for various structural and artisanal uses.

The bark of *Xylopia aethiopica* has found its way into the crafting of doors and partitions. This application underscores the resourcefulness of local communities, utilizing natural materials for essential components in construction. The wood of the plant, noted for its resilience against termite attacks, has become a preferred choice in hut construction. Its durability is evident in its use for posts, scantlings, roof-ridges, and joists, contributing to the robustness and longevity of traditional dwellings (Erhirhie and Moke 2014),

Beyond terrestrial structures, *Xylopia aethiopica* wood has proven valuable in the construction of watercraft. The wood's inherent strength and resistance to environmental elements make it suitable for crafting boat components such as masts, oars, paddles, and spars. This dual-purpose application reflects the

versatility of the plant in meeting the practical needs of communities residing in regions where *Xylopia aethiopica* is abundant (Erhirhie and Moke 2014), In Togo and Gabon, the wood from *Xylopia aethiopica* has a historical association with weaponry. The plant's wood has traditionally been fashioned into bows and crossbows, serving the needs of hunters and warriors. This cultural application not only highlights the plant's role in crafting essential tools for subsistence but also emphasizes its cultural significance in the context of traditional practices related to hunting and defense (Erhirhie and Moke 2014), The documented uses of *Xylopia aethiopica* in construction and craftsmanship, as discussed by Erhirhie and Moke (2014), provide valuable insights into the plant's multifaceted contributions to the livelihoods and cultural practices of local communities. This utilization of natural resources showcases the symbiotic relationship between humans and their environment, emphasizing the sustainable utilization of plant resources for both practical and cultural purposes.

2.1.6 Pharmacological Uses of *Xylopia aethiopica*

The dried fruits of *Xylopia aethiopica* play a dual role in both culinary and medicinal realms, as documented by Okonkwo *et al.* in 2021. In traditional practices, these dried fruits are utilized as a spice, enhancing the flavor profile of various dishes. Simultaneously, the plant's medicinal potential is recognized, with

the dried fruits being employed in herbal medicine for their therapeutic properties. One notable aspect of *Xylopia aethiopica*'s medicinal attributes, as elucidated by Okonkwo *et al.* (2021), is its anti-inflammatory action, particularly in the context of acute inflammation. This finding adds scientific support to the plant's traditional use in mitigating inflammatory conditions, underscoring its potential as a natural remedy for ailments associated with inflammation.

Furthermore, Okonkwo *et al.* (2021) shed light on hormonal modulation attributed to *Xylopia aethiopica*. The study reveals a significant increase in Follicle Stimulating Hormone (FSH) and Progesterone levels in treated groups. This hormonal impact suggests potential applications in reproductive health and hormonal balance.

The comprehensive study by Okonkwo and colleagues expands the understanding of the multifaceted benefits of *Xylopia aethiopica*. From its traditional role as a culinary spice to its scientifically supported anti-inflammatory properties and hormonal effects, the plant emerges as a valuable resource in both traditional and modern medicinal contexts. The integration of traditional knowledge with contemporary scientific findings paves the way for exploring *Xylopia aethiopica*'s potential contributions to holistic healthcare practices.

2.1.7 Phytochemicals present in *Xylopia aethiopica*

Plant part	Alkaloids	Saponins	Tannins	Reducing Sugar	Phloba-tannin	Anthraquinone	Steriods	Flavonoids	Glycosides
Petiole	+	+	+	-	-	+	+	+	+
Seed	+	+	-	-	-	-	+	+	-
Leaf	+	+	+	-	-	-	+	+	-
Bark	+	+	-	+	-	+	-	+	+
Root	-	-	-	+	-	-	-	-	-

+ = presence. - = absence of bioactive compound

Phytochemicals as antioxidants play vital roles in human health (Ivan, 2003; Adesegun *et al.*, 2008; Yusuf *et al.*, 2014). *Xylopia aethiopica* has been found to contain some phytochemicals which exhibit a wide range of biological effects as a consequence of their antioxidant properties (Fleischer, 2003; Keita *et al.*, 2003). The chemical components of *Xylopia aethiopica* have been helpful in the avoidance and treatment of cancerous tumors.

An alkaloid is a type of plant derived organic compound. Alkaloids are generally composed of oxygen, hydrogen, carbon and nitrogen. Some alkaloids are considered toxic but others are often used medicinally (Ivan, 2003; Yusuf *et al.*, 2014). Many alkaloids can be used for medical purposes (Fleischer, 2003; Keita *et al.*, 2003). Atropine for instance is used to stimulate the central nervous system and to dilate the pupils of the eyes (Keita *et al.*, 2003). Anonecaine, an alkaloids constituent of X. aethiopica, is known to have anti-pyretic effect. They are powerful antibiotics and valuable medicine against malaria as well as their application in local anesthesia as pain relief (Aguoru *et al.*, 2016; Evans, 2009; Gang, 2010).

Flavonoids represent the most common and widely distributed of plant phenolics found in *Xylopia aethiopica*. Flavonoids prevent oxidative cell damage, have strong anti-cancer activity and protects against all stages of carcinogenesis (Keita *et al.*, 2003; Yusuf *et al.*, 2014; Aguoru and Olasan, 2014). As antioxidants, flavonoids from *Xylopia aethiopica* provide anti-inflammatory action. Flavonoids are important antioxidants and promote several health effects. Aside from antioxidant activity, these molecules provide the following beneficial effects; antiviral, anti-cancer, anti-inflammatory and anti-allergic (Fleischer, 2003). Saponins another phytochemical constituent of *Xylopia aethiopica* have wide range of biological properties, they are used to recover homeostasis, have anti- inflammatory and anti-

cancer actions. Saponins cause a reduction of blood cholesterol by preventing its re-absorption. They have antitumor and ant mutagenic activities and can lower the risk of human cancers by preventing cancer cells from growing apart from their biocidal effects against pathogens (Morisaki *et al.*, 1995; Fleischer, 2003; Evans, 2009; Yusuf *et al.*, 2014; Aguoru and Olasan, 2014).

2.1.8 *Xylopia aethiopica* in Pregnancy

Xylopia aethiopica, a plant with deep-rooted traditional applications, extends its influence into the realms of reproductive health, as highlighted by Abolaji *et al.* in 2007 and Adodo and Iwu in 2020. In the context of maternal care, *Xylopia aethiopica* has been traditionally utilized to enhance lactation, aiming to boost milk production and thereby encouraging breastfeeding. This practice holds significance not only for infant nourishment but also due to its impact on inhibiting ovulation, as demonstrated in studies by Abolaji and colleagues.

The traditional use of *Xylopia aethiopica* as a galactagogue, promoting the secretion of breast milk, aligns with the cultural and historical practices aimed at ensuring optimal infant nutrition. The documented influence on inhibiting ovulation emphasizes the plant's role in traditional contraception methods. This dual functionality suggests that *Xylopia aethiopica*, beyond its nutritional benefits

for infants, plays a role in family planning practices by affecting reproductive processes.

On the male reproductive front, Abolaji *et al.* (2007) provide insights into the plant's use in reducing sperm quality parameters when consumed as a concoction derived from Uda seeds. This traditional application indicates a potential impact on male fertility, and it underlines the diverse ways in which *Xylopia aethiopica* is integrated into cultural practices related to reproductive health and family planning.

While *Xylopia aethiopica* exhibits notable effects on lactation and male reproductive health, caution is advised during pregnancy, as recommended by Adodo and Iwu in 2020. The warning aligns with the traditional knowledge that has been passed down through generations, emphasizing the need to avoid the use of *Xylopia aethiopica* during pregnancy. This precautionary measure suggests potential effects that may interfere with the delicate processes of gestation.

2.1.9 *Xylopia aethiopica* in Reproductive Hormones

Scientific investigations into the effects of dietary *Xylopia aethiopica* shed light on its potential impact on reproductive hormones, offering intriguing insights into its physiological mechanisms. A study conducted by Onyebuagu *et al.* in 2013 revealed a noteworthy observation – the consumption of *Xylopia aethiopica* was associated with a reduction in plasma levels of steroid reproductive hormones. This

intriguing finding suggests a potential link between the plant's dietary intake and hormonal regulation, with a proposed mechanism involving a reduction in plasma cholesterol levels. The study points towards the intricate interplay between diet, cholesterol metabolism, and reproductive hormone regulation, offering a foundation for further exploration into the specific pathways involved.

Furthermore, an independent study by Okonkwo *et al.* in 2021 builds on the understanding of *Xylopia aethiopica*'s influence on reproductive hormones. This research demonstrates a significant increase in Follicle Stimulating Hormone (FSH) and Progesterone levels in treated groups. The augmentation of these key reproductive hormones underscores the plant's potential in modulating hormonal balance. The increase in FSH, crucial for stimulating the maturation of ovarian follicles in females, and Progesterone, essential for maintaining a healthy reproductive environment, suggests a potential role for *Xylopia aethiopica* in promoting reproductive health.

These studies collectively contribute to a nuanced understanding of *Xylopia aethiopica*'s effects on reproductive physiology. The dual findings – a reduction in steroid reproductive hormones by Onyebuagu *et al.* (2013) and an increase in FSH and Progesterone by Okonkwo *et al.* (2021) – highlight the complexity of the plant's interactions within the endocrine system. It prompts further exploration into

the specific compounds present in *Xylopia aethiopica*, their modes of action, and the implications for overall reproductive health.

The studies conducted by Onyebuagu *et al.* (2013) and Okonkwo *et al.* (2021) contribute valuable data to the growing body of knowledge surrounding the physiological effects of *Xylopia aethiopica*. The contrasting outcomes suggest that the plant's impact on reproductive hormones may be context-dependent, emphasizing the need for comprehensive research to unravel the intricate mechanisms at play. These findings stimulate curiosity and provide a foundation for future investigations into the potential therapeutic applications of *Xylopia aethiopica* in the context of reproductive health

.2.1.10 Xylopia aethiopica in Prostaglandin

Ezekwesili *et al.* (2010) delved into the intricate biochemical activities of *Xylopia aethiopica*, specifically exploring the lipid and methanol extracts of the plant and their effects on prostaglandin synthesis. Their study yielded compelling results that contribute to the understanding of *Xylopia aethiopica*'s pharmacological properties. In their investigation, Ezekwesili and colleagues observed that the lipid extract of *Xylopia aethiopica* demonstrated a distinct prostaglandin synthetase substrate activity. This finding implies that the lipid extract serves as a substrate for prostaglandin synthetase, suggesting a potential role in the intricate cascade of

prostaglandin synthesis within the body. Prostaglandins are bioactive lipid compounds known for their diverse physiological roles, including inflammation regulation, blood flow modulation, and reproductive processes.

Simultaneously, the study revealed another facet of *Xylopia aethiopica*'s biochemical influence. The methanol extract of the plant was found to enhance the synthesis of prostaglandins, utilizing *Xylopia aethiopica* oil as a substrate. This signifies that the methanol extract has a stimulating effect on the enzymatic processes involved in prostaglandin production. The use of *Xylopia aethiopica* oil as a substrate further connects the findings to the plant's natural composition, emphasizing the relevance of its constituents in mediating these biochemical activities.

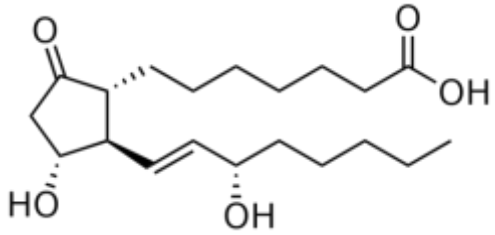
These observations contribute significantly to the understanding of *Xylopia aethiopica*'s pharmacodynamics, suggesting a potential role in modulating prostaglandin synthesis. Prostaglandins play pivotal roles in various physiological functions, making this plant a subject of interest for further exploration in the context of inflammation regulation, vascular homeostasis, and reproductive health. Ezekwesili *et al.* (2010) research provides a biochemical lens through which the lipid and methanol extracts of *Xylopia aethiopica* are scrutinized for their impact on prostaglandin synthesis. The findings underscore the intricate bioactivity of the

plant's constituents and stimulate curiosity regarding its potential pharmacological applications, offering a foundation for future studies aimed at unraveling the specific molecular mechanisms involved in *Xylopia aethiopica*'s modulation of prostaglandin pathways.

2.2 PROSTAGLANDIN

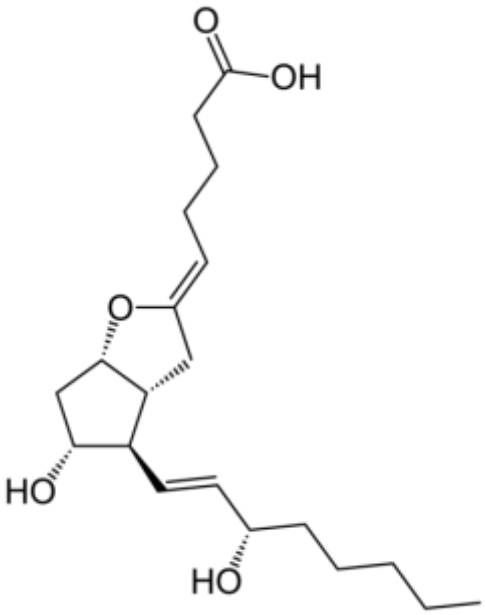
2.2.1. Description of prostaglandin

Prostaglandins (PG) are a group of physiologically active lipid compounds called eicosanoids (Ricciotti and FitzGerald, 2011) having diverse hormone-like effects in animals. Prostaglandins have been found in almost every tissue in humans and other animals. They are derived enzymatically from the fatty acid arachidonic acid (Ricciotti and FitzGerald, 2011). Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring. They are a subclass of eicosanoids and of the prostanoid class of fatty acid derivatives.



E 1 – Alprostadil Calvero

(2006).



I 2 – Prostacyclin

Benjah (2011).

The structural differences between prostaglandins account for their different biological activities. A given prostaglandin may have different and even opposite effects in different tissues in some cases. The ability of the same prostaglandin to stimulate a reaction in one tissue and inhibit the same reaction in another tissue is determined by the type of receptor to which the prostaglandin binds. They act as autocrine or paracrine factors with their target cells present in the immediate vicinity of the site of their secretion. Prostaglandins differ from endocrine hormones in that they are not produced at a specific site but in many places throughout the human body. Prostaglandins are powerful, locally-acting

vasodilators and inhibit the aggregation of blood platelets. Through their role in vasodilation, prostaglandins are also involved in inflammation. They are synthesized in the walls of blood vessels and serve the physiological function of preventing needless clot formation, as well as regulating the contraction of smooth muscle tissue (Nelson, 2005) Conversely, thromboxanes (produced by platelet cells) are vasoconstrictors and facilitate platelet aggregation. Their name comes from their role in clot formation (thrombosis). Specific prostaglandins are named with a letter indicating the type of ring structure, followed by a number indicating the number of double bonds in the hydrocarbon structure. For example, prostaglandin E1 has the abbreviation PGE_1 and prostaglandin I_2 has the abbreviation PGI_2

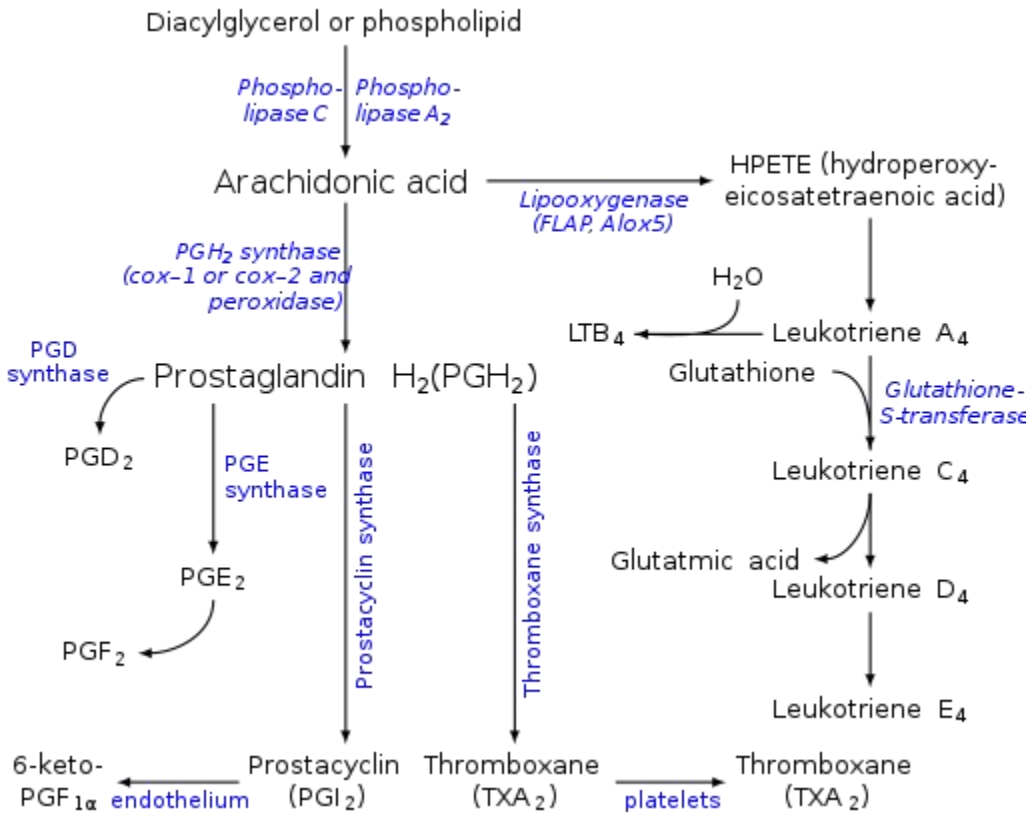
2.2.2 History and Name

Systematic studies of prostaglandins began in 1930, when Kurzrock and Lieb found that human seminal fluid caused either stimulation or relaxation of strips of isolated human uterus. They noted the curious finding that uteri from patients who had gone through successful pregnancies responded to the fluid with relaxation, while uteri from sterile women responded with contraction upon addition of this seminal fluid (Kurzrok and Lieb, 1930) The name prostaglandin derives from the prostate gland, chosen when prostaglandin was first isolated from seminal fluid in 1935 by the Swedish physiologistUlf von Euler (Euler,

1935) and independently by the Irish-English physiologist Maurice Walter Goldblatt (1895–1967) (Goldblatt, 1935) Prostaglandins were believed to be History and name part of the prostatic secretions, and eventually were discovered to be produced by the seminal vesicles. Later, it was shown that many other tissues secrete prostaglandins and that they perform a variety of functions. The first total syntheses of prostaglandin $F_{2\alpha}$ and prostaglandin E_2 were reported by E. J. Corey in 1969 (Nicolaou and Sorensen,1996) an achievement for which he was awarded the Japan Prize in 1989. In 1971, it was determined that aspirin-like drugs could inhibit the synthesis of prostaglandins. The biochemists Sune K. Bergström, Bengt I. Samuelsson and John R. Vane jointly received the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.

2.2.3 BIOCHEMISTRY

2.2.3.1 Biosynthesis



Biosynthesis of eicosanoids (Krishnavedala, 2020).

Prostaglandins are found in most tissues and organs. They are produced by almost all nucleated cells. They are autocrine and paracrine lipid mediators that act upon platelets, endothelium, uterine and mast cells.

They are synthesized in the cell from the fatty acid arachidonic acid (Ricciotti and FitzGerald, 2011). Biochemistry Arachidonic acid is created from diacylglycerol via phospholipase-A2, then brought to either the cyclooxygenase pathway or the lipoxygenase pathway. The cyclooxygenase pathway produces thromboxane, prostacyclin and prostaglandin D, E and F. Alternatively, the lipoxygenase enzyme pathway is active in leukocytes and in macrophages and synthesizes leukotrienes.

2.2.3.2 Release of prostaglandins from the cell

Prostaglandins were originally believed to leave the cells via passive diffusion because of their high lipophilicity. The discovery of the prostaglandin transporter (PGT, SLCO2A1), which mediates the cellular uptake of prostaglandin, demonstrated that diffusion alone cannot explain the penetration of prostaglandin through the cellular membrane. The release of prostaglandin has now also been shown to be mediated by a specific transporter, namely the multidrug resistance protein 4 (MRP4, ABCC4), a member of the ATPbinding cassette transporter superfamily. Whether MRP4 is the only transporter releasing prostaglandins from the cells is still unclear.

2.2.3.3 Cyclooxygenases

- Prostaglandins are produced following the sequential oxygenation of arachidonic acid, DGLA or EPA by cyclooxygenases (COX-1 and COX-2) and terminal prostaglandin synthases. The classic dogma is as follows:

  COX-1 is responsible for the baseline levels of prostaglandins.COX-2 produces prostaglandins through stimulation. However, while COX-1 and COX-2 are both located in the blood vessels, stomach and the kidneys, prostaglandin levels are increased by COX-2 in scenarios of inflammation and growth.

2.2.3.4 Prostaglandin E synthase

Prostaglandin E_2 (PGE_2) — the most abundant prostaglandin (Ke *et al.*, 2016) — is generated from the action of prostaglandin E synthases on prostaglandin H_2 (prostaglandin H_2, PGH_2). Several prostaglandin E synthases have been identified. To date, microsomal (named as misoprostol) prostaglandin E synthase-1 emerges as a key enzyme in the formation of PGE_2.

2.2.3.5 Other terminal prostaglandin synthases

Terminal prostaglandin synthases have been identified that are responsible for the formation of other prostaglandins. For example, hematopoietic and lipocalin prostaglandin D synthases (hPGDS and lPGDS) are responsible for the formation

of PGD_2 from PGH_2. Similarly, prostacyclin (PGI_2) synthase (PGI_S) converts PGH_2 into PGI+. A thromboxane synthase (TxAS) has also been identified. Prostaglandin-F synthase (PGFS) catalyzes the formation of 9α,11β-$PGF_{2\alpha,\ \beta}$ from PGD_2 and $PGF_{2\alpha}$ from PGH_2 in the presence of NADPH. This enzyme has recently been crystallized in complex with PGD_2 (Komoto *et al.*, 2004) and bimatoprost (Komoto *et al.*, 2006) (a synthetic analogue of $PGF_{2\alpha}$).

2.2.4 Functions of Prostaglandins.

There are currently ten known prostaglandin receptors on various cell types. Prostaglandins ligate a subfamily of cell surface seven-transmembrane receptors, G-protein-coupled receptors. These receptors are termed DP1-2, EP1-4, FP, IP1-2, and TP, corresponding to the receptor that ligates the corresponding prostaglandin (e.g., DP1-2 receptors bind to PGD_2). The diversity of receptors means that prostaglandins act on an array of cells and have a wide variety of effects such as:

- create eicosanoids hormones acts on thermoregulatory center of hypothalamus to produce fever
- increases mating behaviors in goldfish (Stacey, 2003)
- Prostaglandins are released during menstruation, due to the destruction of the endometrial cells, and the resultant release of their contents (Lethaby *et*

al.,2013) Release of prostaglandins and other inflammatory mediators in the uterus cause the uterus to contract. These substances are thought to be a major factor in primary dysmenorrhea (Wright and Wyatt, 2003; Harez, 2006; Rodriguez *et al.*, 2019).

2.2.5 G-Protein activation by Prostaglandin synthesis

When prostaglandins receptors on membrane activate G-protein, various effector enzymes are activated, the specific effector enzyme activated can be dependent on the type of G-protein and the cellular context. However, commonly activated effector enzymes include: **Adenylyl Cyclase (AC):** This enzyme is involved in the production of cyclic AMP (cAMP), a second messenger that plays a crucial role in many biological processes (Malik and Dua, 2024).

Phospholipase Cβ (PLCβ): This enzyme catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG), both of which act as second messengers (Malik and Dua, 2024).

Ion Channels: Certain G proteins can also regulate the activity of ion channels, affecting the flow of ions like Na^+, K^+, and Ca^{2+} across the cell membrane (Marinissen and Gutkind, 2001).

In the context of prostaglandins, they often interact with G proteins that stimulate the enzyme Phospholipase C (PLC). This leads to the production of inositol trisphosphate (IP3) and diacylglycerol (DAG), which serve as second messengers within the cell (Marinissen and Gutkind, 2001). It's important to note that the activation of these enzymes leads to a cascade of events within the cell, ultimately resulting in a physiological response. The specific response will depend on the cell type and the nature of the initial signal (Cabrera-

Vera *et al*., 2003; Marinissen and Gutkind, 2001).

2.2.6 Types of Prostaglandins

The following is a comparison of different types of prostaglandin, including prostaglandin I_2 (prostacyclin; PGI_2), prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Moreno, 2017).

Type	Receptor	Receptor type	Effects	Factors	Mechanism of Action	Roles at different pregnancy stages and conditions
PGI_2	IP	G_s	Vasodilation Inhibit platelet aggregation Bronchodilation	Type 2 inflammation (Oyesola and Tait-Wojno, 2021) Endotheliumdependent regulation (Goa, 2022)	When activated by PGI2, IP (prostacyclin receptor) stimulates adenyl cyclase leading to increased intracellular cyclic AMP (cAMP). Increased	**Normal Pregnancy**: In Prostaglandin I_2 (PGI_2) during normal pregnancy can have several effects. PGI_2 is known to cause vasodilation, and this can contribute to the decrease in systemic vascular resistance observed during

					cAMP then leads to activation of protein kinase A (PKA) and further phosphorylation of key proteins (Harada*et al*., 1997)	pregnancy (Physiopedia, 2023). Additionally, the increased metabolic rate of the combined mother/fetus organism leads to an increase in total O_2 consumption and CO_2 production (Yartsev, 2015). This could potentially lead to a persistent hypoxia and

						mild respiratory acidosis, which would lead to a slight increase in respiratory rate and a raised HCO3-. However, expectant mothers blow off vast amounts of CO_2 and actually generate a mild respiratory alkalosis (Yartsev, 2015).

						Miscarriage: it's known that low progesterone levels have been associated with an increased rate of miscarriage (Feferkorn and Tulandi, 2021). Progesterone is critical for the maintenance of pregnancy and its decrease can lead to miscarriage unless exogenous progesterone is administered (Feferkorn and Tulandi, 2021). **Preterm Labor**: It's known that unbalanced progesterone signals may cause some

						pregnant women to experience preterm labor (Peavey *et al*., 2021). Prostaglandins PGE_2 probably increase the chance of vaginal delivery in 24 hours, they increase uterine hyperstimulation with fetal heart changes but do not affect or may reduce caesarean section rates (Thomas *et al*., 2014).

PGD_2	PTGDR (DP1) and CRTH2 (DP2)	GPCR	Produced by mast cells; recruits Th2 cells, eosinophils, and basophils In mammalian organs, large amounts of PGD2	Type 2 inflammation (Domingo *et al*., 2018). Mast cell activation	PGD_2 binds to the receptor PTGDR (DP_1), as well as CRTH2 (DP_2) (Garza *et al*., 2012). It is a major prostaglandin produced by mast cells and recruits Th2	**Normal Pregnancy**: it is known that pregnancy is characterized by a series of metabolic changes that promote adipose tissue accretion in early gestation, followed by insulin resistance and facilitated lipolysis in late pregnancy (Barbour *et al*., 2007). In early pregnancy, insulin secretion increases, while insulin sensitivity is unchanged,

					cells,	

			are found only in the brain and in mast cells Critical to development of allergic diseases such as asthma	(Domingo *et al*., 2018).	eosinophils, and basophils (Morrow *et al*., 1989)	decreased, or may even increase (Barbour *et al*., 2007). However, in late gestation, maternal adipose tissue depots decline, while postprandial free fatty acid (FFA) levels increase and insulinmediated glucose disposal worsens by 40–60% compared with pre-pregnancy (Barbour *et al*., 2007). **Miscarriage**: it is known that low progesterone levels have been associated with an increased rate of miscarriage

						(Feferkorn and Tulandi, 2021). Progesterone is critical for the maintenance of pregnancy and its decrease can lead to miscarriage unless exogenous progesterone is administered (Feferkorn and Tulandi, 2021). **Preterm Labor**: it is known that unbalanced progesterone signals may cause some pregnant women to experience preterm labor (Peavey *et al*., 2021). Prostaglandins PGE_2 probably increase the chance of

						vaginal delivery in 24 hours, they increase uterine hyperstimulation with fetal heart changes but do not affect or may reduce caesarean section rates (Thomas *et al*., 2014).

PGE_2	EP_1	G_q	Bronchoconstriction GI tract smooth muscle contraction	Hypercapnia (Uekawa *et al*., 2016). Inflammation (Ricciotti and FitzGerald, 2011).	EP_1 receptors are G-protein-coupled receptors. When activated by PGE2, they stimulate a reduction in cyclic AMP (cAMP) levels, leading	**Normal Pregnancy**: PGE2 plays a crucial role in various stages of pregnancy. It is involved in ovulation, fertilization, embryo development, and early implantation (Niringiyumukiza *et al*., 2018). High levels of PGE2 are present throughout late pregnancy, not just during childbirth (Guo *et al*., 2019).

					to various downstream effects (Biringer, 2020).	It reduces extracellular matrix viscosity, thereby optimizing conditions for sperm penetration (Niringiyumukiza *et al*., 2018). It also maintains

	EP_2	G_s	Bronchodilation GI tract smooth muscle relaxation Vasodilation	Hypercapnia (Uekawa *et al*., 2016). Inflammation (Ricciotti and FitzGerald, 2011). UV irradiation (Ricciotti and FitzGerald,	EP_2 is a G-protein coupled receptor which leads to the activation of adenyl cyclase and increases levels of cyclic AMP (cAMP), which can drive protein	luteal function for embryo development and early implantation (Niringiyumukiza *et al*., 2018). **Miscarriage**: PGE_2 is an active contractile agent and are effective in uterine evacuation for mid-trimester abortion or fetal demise (Wiley *et al.,* 1989). **Preterm Labor**: PGE_2 is thought to be an

				2011).	kinase A (PKA) or exchange factor directly activated by cAMP (EPAC)-dependent signaling, depending on the cell type (Quan *et al*., 2013)	important mediator in the initiation of human labor (Wood *et al*., 2021). It increases uterine hyperstimulation with fetal heart changes but does not affect or may reduce caesarean section rates

	EP_3	G_i	↓ gastric acid secretion ↑ gastric mucus secretion uterus contraction (when pregnant) GI tract smooth muscle contraction lipolysis inhibition ↑ autonomic		Most human EP_3 isoforms inhibit cyclic AMP (cAMP) generation via Gi-protein. Some isoforms can also increase intracellular calcium like EP_1, and some	(Thomas *et al*., 2014). It also increases the likelihood of cervical change, with no increase in operative delivery rates (Thomas *et al*., 2014).

			neurotransmitters (Rang, 2003) ↑ platelet response to their agonists (Fabre *et al*., 2001) and ↑ atherothrombosis in vivo (Gross *et al*., 2007)		might also signal via Gs proteins (Semmlinger *et al*., 2018). Activation of EP_3 increases intracellular Ca^{2+} via phospholipase C (PLC) and/or inhibits cAMP	

					production via adenylate cyclase (Bakker *et al*., 2017).	
	Unspecified		Hyperalgesia (Rang,			

			2003) pyrogenic			

$PGF_{2\alpha}$	FP	G_q	Uterus contraction Bronchoconstriction Urinary bladder contractions (Stromberga *et al.*, 2020) Vasoconstriction in cerebral circulation (Venkatraghavan *et al.,* 2018)	Inflammation and Cardiovascular homeostasis (Zhang *et al*., 2010). Female reproductive function (Zhang *et al*., 2010). COX enzymes (Zhang *et al*., 2010).	PGF2α exerts its actions through receptor-mediated stimulation of the phospholipase C-intracellular calcium-PKC pathway and activation of downstream protein kinases, such as extracellular regulated protein kinase (ERK),	**Normal Pregnancy**: P increase as pregnancy progresses (Wood *et al*., 2021). It plays a crucial role in preparing the uterus for the onset of labor (Xu *et al*., 2013). It also promotes embryo implantation and development (Kaczynski *et al*.,

					calcium/calmodulindependent protein kinase II (CaMKII), and 5′-adenosine	2018). **Miscarriage**: PGF2α result in a pathological course of pregnancy or pregnancy failure (Zhu *et al*., 2023). Also, locally-acting PGF2α plays a luteoprotective role by inhibiting apoptosis and necroptosis in the early corpus luteum

						(Jonczyk *et al*., 2019).

					monophosphateactivated protein kinase (AMPK) (Plewes *et al*., 2023)	**Preterm Labor**: PGF2α is thought to be an important mediator in the initiation of human labor (Wood *et al*., 2021). It increases the expression of uterine activation proteins in pregnant human myometrial cells (Xu *et al*., 2013).

2.2.7 The Role of Prostaglandins on Female Reproduction

Prostaglandins (PGs) are lipid compounds that play a crucial role in various physiological processes, including female reproduction (Sugimoto *et al*., 2014; Ye *et al*., 2020). This article aims to elucidate the role of prostaglandins in female reproductive processes such as ovulation, fertilization, and parturition.

Prostaglandins and Ovulation

Prostaglandins are known to regulate the female reproductive system and are involved in the control of ovulation (Niringiyumukiza *et al*., 2018). They can cause changes in the consistency of cervical mucus, making it more receptive to sperm. This helps facilitate the transportation and survival of sperm in the female reproductive system (Schjenken and Robertson, 2020).

Prostaglandins and Fertilization

A series of studies using EP2-deficient mice demonstrated that after ovulation, chemokine signaling in the cumulus cells stimulates integrin activation and cumulus extracellular matrix (ECM) assembly through the RhoA/ROCK/actomyosin pathway (Sugimoto *et al*., 2014). However, excessive chemokine signaling can disturb sperm penetration. PGE2-EP2 signaling suppresses such chemokine signaling and stimulates cumulus ECM disassembly, contributing to successful fertilization (Sugimoto *et al*., 2014).

Prostaglandins and Parturition

Prostaglandins also play a significant role in parturition. Studies using FP-deficient mice revealed that PGF2α-FP signaling induces parturition at least by terminating progesterone production (Sugimoto *et al*., 2014). However, some other EP signals are likely to be involved in parturition by inducing myometrial contraction (Sugimoto *et al*., 2014). Therefore, it is crucial to clarify w hich EP and/or FP receptor signals are physiologically essential for myometrial contraction and successful parturition

(Sugimoto *et al*., 2014).

2.2.8 Role in pharmacology Inhibition

Examples of prostaglandin antagonists are:

- NSAIDs (inhibit cyclooxygenase) and COX-2 selective inhibitors or coxibs
- Corticosteroids (inhibit phospholipase A_2 production)
- Cyclopentenone prostaglandins may play a role in inhibiting inflammation
- Vitamin D_3 and vitamin K_2 (Kieronska-Rudek *et al.*, 2021; Koshihara *et al.*, 1993; Krishnan *et al.*, 2009).

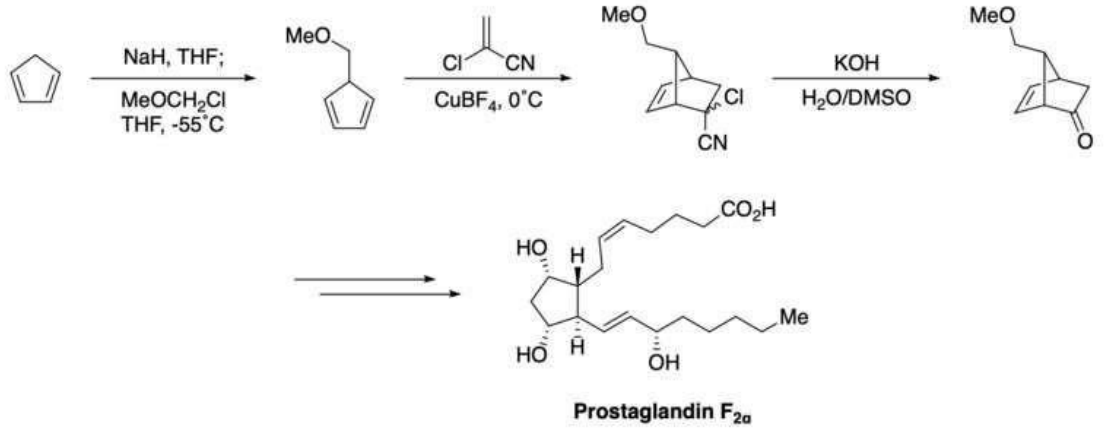
2.2.9 Clinical uses

Synthetic prostaglandins are used:

- To induce childbirth (parturition) or abortion (PGE_2 or $PGF_{2(misoprostol)}$, with or without mifepristone, a progesterone antagonist).
- Induction of labour (W.H.O, 2011).
- To prevent closure of ductus arteriosus in newborns with particular cyanotic heart defects (PGE_1)
- As a vasodilator in severe Raynaud syndrome or ischemia of a limb.
- In pulmonary hypertension.
- In treatment of glaucoma (as in bimatoprost ophthalmic solution, a synthetic prostamide analog with ocular hypotensive activity) ($PGF_{2\alpha}$)
- To treat erectile dysfunction or in penile rehabilitation following surgery (PGE_1 as alprostadil) (Schifano *et al*., 2022).
- To measure erect penis size in a clinical environment (Veale *et al.*, 2015)

2.2.10 Synthesis

The original synthesis of prostaglandins $F_{2\alpha}$ and E_2 is shown below. It involves a Diels–Alder reaction which establishes the relative stereochemistry of three contiguous stereocenters on the prostaglandin cyclopentane core (Koda-Kimble, 2007).



(Koda-Kimble, 2007)

2.3 Sabinene:

2.3.1 Description

Sabinene is a naturally occurring bicyclic monoterpene, as highlighted by Verma *et al*. (2016). Its molecular formula is represented as C10H16, and it is distinguished by a unique structural arrangement comprising a strained ring system, wherein a cyclopentane ring is fused to a cyclopropane ring (Verma *et al*., 2016). This intriguing compound is predominantly found in the essential oils extracted from various plants, including Marjoram, holm oak (Quercus ilex), and Norway spruce (Picea abies) (Verma *et al*., 2016).

2.3.2 Common Name of Sabinene

The common name for this compound is Sabinene (Verma *et al*., 2016). Other names include 1-Isopropyl- 4-methylenebicyclo (3.1.0) hexane, 4 (10)-Thujene, Sabinen, (+)-Sabinene, THUJENE, 4 (10)-, and α- Sabinene (Wang *et al*., 2021).

2.3.3 Foods and Fruits Containing Sabinene

Sabinene, as highlighted by Baron (2018), is widely distributed across various foods and fruits, owing to its presence in a multitude of natural sources. This terpene is notably found in holm oak trees, spruce trees, juniper bushes, clove plants, and spices such as black pepper and nutmeg (Baron, 2018). Its occurrence in these diverse botanical sources underscores its broad ecological distribution and

significance in plant metabolism. Moreover, sabinene plays a pivotal role in determining the characteristic spiciness of black pepper, as noted by Verma *et al*. (2016). This compound serves as a major constituent in carrot seed oil, contributing to its aromatic profile and potential therapeutic properties (Verma *et al*., 2016). Although present in relatively low concentrations, sabinene is also detected in tea tree oil, further emphasizing its widespread occurrence in essential oils (Verma *et al*., 2016).

Further highlighting its versatility, sabinene is identified as a component in the essential oils extracted from nutmeg, Laurus nobilis, and Clausena anisate, as detailed by Verma *et al*. (2016).

2.3.4 Effect of Sabinene on Prostaglandins

Prostaglandins, as elucidated by Fajrin *et al*. (2020), are bioactive lipid compounds that function akin to hormones, exerting influence over various physiological processes such as inflammation, pain modulation, and uterine contractions. While direct evidence linking sabinene to prostaglandins remains lacking, it is noteworthy that sabinene has been found to possess anti-inflammatory properties, as highlighted by Baron (2018). Given that inflammation often involves the action of prostaglandins, as mentioned by Fajrin *et al*. (2020), it is conceivable that sabinene may indirectly modulate prostaglandin activity through its anti-inflammatory effects.

The anti-inflammatory properties attributed to sabinene suggest its potential to mitigate the inflammatory response, which could have downstream effects on prostaglandin activity. By reducing inflammation, sabinene may indirectly influence the synthesis or action of prostaglandins, as proposed by Fajrin *et al*. (2020).

(Kim *et al,* 2013.) investigating the effect of sabinene contained in Hallabong flower oil on Lipopolysaccharide (LPS)- stimulated RAW 264.7 macrophage cells, reported that sabinene contained in Hallabong oil were found to inhibit nitric oxide and prostaglandin E2 production in an in vivo study.

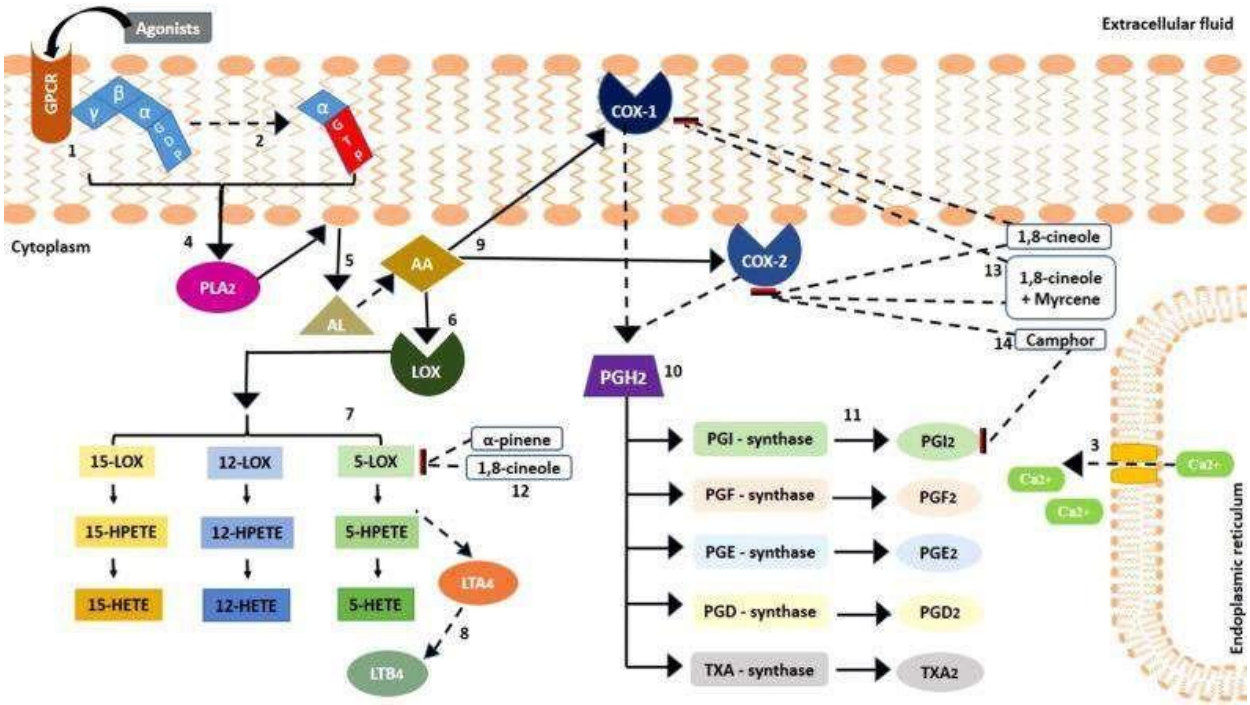
2.3.5 Mechanism of Action on Prostaglandin

While the specific action of sabinene on prostaglandin synthesis is not detailed, it is plausible that sabinene could also affect the cyclooxygenase (COX) enzymes, similar to nonsteroidal anti-inflammatory drugs (NSAIDs). COX enzymes are responsible for the conversion of arachidonic acid to prostaglandins, which are lipid compounds that play a key role in inflammation and pain (Osafo *et al*., 2017; Rainsford, 2012).

By inhibiting COX enzymes, sabinene could potentially reduce the production of prostaglandins, hereby exerting an anti-inflammatory effect (Zhang *et al*., 2020). In the study of Takaki *et al*. (2008), the anti-inflammatory effect of EORO was due to the presence of 1,8-cineole with possibly synergistic action with myrcene, and at

least partially due to inhibition of prostaglandin synthesis or release of other endogenous mediators.

Inhibition of arachidonic acid cascade enzymes



(Takaki *et al*., 2008)

2.4 Terpinen-4-ol:

2.4.1 Description

Terpinen-4-ol, alternatively known as Sterpene-4-ol, is a naturally occurring monoterpene, as elucidated by Şahin *et al*. (2023). With a molecular formula represented as C10H18O, this compound is distinguished by its structure based on the o-, m-, or p-menthane backbone, as highlighted by Mani *et al*. (2021). Terpinen4-ol stands out as a primary constituent of tea tree oil, derived from the leaves, branches, and bark of Melaleuca alternifolia Cheel, as detailed by Şahin *et al*. (2023).

This compound's presence as a major component of tea tree oil underscores its significance in the aromatic and therapeutic properties associated with this essential oil (Mani *et al*., 2021). Extracted from various parts of the Melaleuca alternifolia plant, terpinen-4-ol contributes to the distinct aroma and potential medicinal benefits attributed to tea tree oil (Şahin *et al*., 2023). Its abundance in this natural extract makes terpinen-4-ol a subject of interest in research exploring the diverse applications of tea tree oil, ranging from skincare products to medicinal formulations (Şahin *et al*., 2023).

2.4.2 Common Name of Terpinen-4-ol

The common name for this compound is Terpinen-4-ol1. Other names include 4Methyl-1-(propan-2-yl) cyclohex-3-en-1-ol, p-Menth-1-en-4-ol, 1-Terpinen-4-ol,4-

Carvomenthenol, 4-Terpineol, 1-Methyl-4isopropyl-1-cyclohexen-4-ol, 4Terpinenol, Terpene-4-ol, Terpinene-4-ol, Para-Menth-1-en-4-ol, 1-paraMenthen-4ol, Terpinenol-4, and Terpinenolu-4 (Wang *et al*., 2021).

2.4.3 Foods and Fruits Containing Terpinen-4-ol

Terpinen-4-ol, as highlighted by Şahin *et al*. (2023), is not only a prominent component of tea tree oil but is also found in various other plants and their essential oils. While specific foods and fruits containing terpinen-4-ol are not explicitly mentioned in the available resources, its widespread occurrence in nature suggests potential presence in certain food items. As a terpene, terpinen-4-ol may contribute to the aroma and flavor of foods in which it is present, albeit in lesser-known quantities compared to its abundance in tea tree oil. The complex blend of volatile compounds, including terpinen-4-ol, found in essential oils derived from plants such as Eucalyptus, lavender, and thyme, hints at the possibility of encountering this compound indirectly through culinary ingredients infused with these oils (Şahin *et al*., 2023).

Furthermore, while terpinen-4-ol may not be a primary flavor component in commonly consumed foods and fruits, its presence in various plant species suggests potential dietary exposure. Studies examining the chemical composition of foods and fruits, particularly those rich in essential oils or known for their aromatic properties, may shed light on the presence of terpinen-4-ol in the diet (Şahin *et al*., 2023).

2.4.4 Effect of Terpinen-4-ol on Prostaglandins

Prostaglandins, as elucidated by Begum *et al*. (2016), are hormone-like substances pivotal in regulating various bodily functions, encompassing inflammation, pain perception, and uterine contractions. Although direct evidence linking terpinen-4-ol to prostaglandins remains scarce, it is noteworthy that terpinen-4-ol has been identified for its anti-inflammatory properties, as underscored by Şahin *et al*. (2023). Considering that inflammation often involves the action of prostaglandins, as highlighted by Begum *et al*. (2016), it is plausible to hypothesize that terpinen-4ol may indirectly modulate prostaglandin activity through its anti-inflammatory effects. The observed anti-inflammatory properties of terpinen-4-ol suggest its potential to attenuate the inflammatory response, which could subsequently influence the synthesis or action of prostaglandins. By mitigating inflammation, terpinen-4-ol may indirectly impact prostaglandin-mediated processes, such as pain perception and uterine contractions, as proposed by Begum *et al*. (2016). (Hart *et*

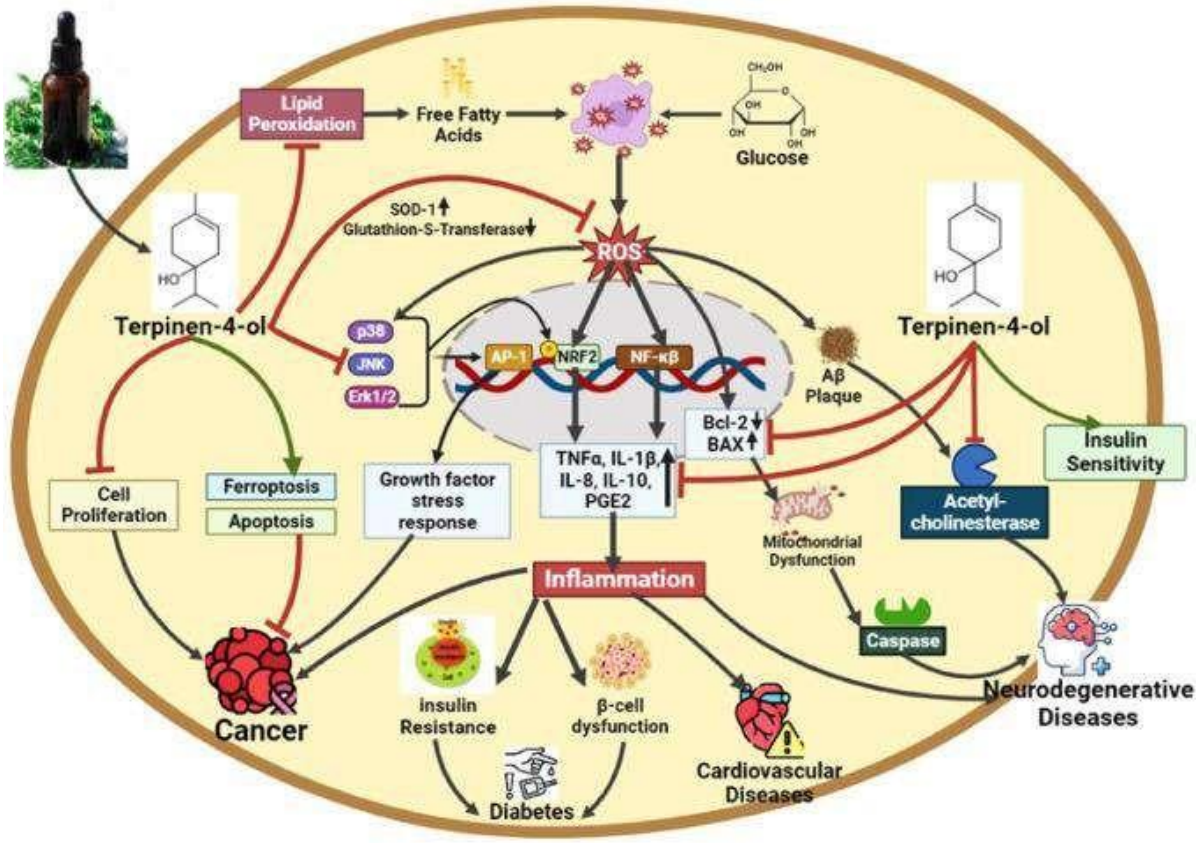
al., 2000) investigating the effect of terpinene-4-ol contained in tea tree oil on lipopolysaccharide (LPS)- activated human peripheral blood monocyte reported that terpinene-4-ol contained in tea tree oil reduce the production of tumour necrosis factor-alpha (TNF alpha), interleukin (IL)-1 beta, interleukin 8, interleukin 10 and prostaglandin E2 (PGE2) in an in vitro study.

2.4.5 Mechanism of Action on Prostaglandin

Terpinen-4-ol has been shown to induce apoptosis rather than necrosis in cancer cells, suggesting that it can trigger programmed cell death (Shapira *et al*., 2016). This indicates that terpinen-4-ol may influence cell signaling pathways that lead to apoptosis, which could include the regulation of inflammatory processes and mediators like prostaglandins (Deen *et al*., 2023).

Prostaglandins are part of the inflammatory response and are synthesized from arachidonic acid through the action of cyclooxygenase (COX) enzymes. If terpinen4-ol inhibits prostaglandin secretion, it may do so by affecting the COX pathway, similar to nonsteroidal anti-inflammatory drugs (NSAIDs). By inhibiting COX enzymes, terpinen-4-ol could potentially reduce the production of prostaglandins, thereby exerting an anti-inflammatory effect (Osafo *et al*., 2017; Rainsford, 2012). Additionally, terpinen-4-ol has demonstrated antimicrobial activity, which includes disrupting the cell membrane and wall integrity of bacteria, leading to cell death (Huang *et al*., 2020). This membrane-disrupting action could

also play a role in its anti-inflammatory effects if similar mechanisms apply to the cells involved in prostaglandin synthesis (Huang *et al*., 2020).



(Deen *et al*., 2023).

2.5 Kaur-16-ol:

2.5.1 Description

Kaur-16-ol, also known as Kaur-16-en-18-ol, is a type of diterpene (Davidson *et al*., 2004). It has a molecular formula of $C_{20}H_{32O}$ and an average mass of 288.467 Da (Davidson *et al*., 2004). This compound is characterized by 6 of 6 defined stereocentres (Davidson *et al*., 2004).

2.5.2 Common Name of Kaur-16-ol

In addition to its primary designation as Kaur-16-ol, this compound is recognized by several alternative names, as documented by Davidson *et al*. (2004) and Ebi (2014). Among these alternate appellations are ()-Kaur-16-en-18-ol, ent-kaur-16-en-19-ol, and Kaurenol. These various nomenclatures reflect different aspects of the compound's chemical structure and stereochemistry, aiding in its precise identification and characterization within scientific literature.

The designation (-)-Kaur-16-en-18-ol denotes the specific stereochemical configuration of the compound, providing insight into the spatial arrangement of its constituent atoms and functional groups. Similarly, entkaur-16-en-19-ol offers additional information regarding the compound's molecular structure, particularly its arrangement within the ent-kaurane class of diterpenoids (Davidson *et al*., 2004).

Furthermore, the term Kaurenol serves as a more generalized descriptor, encompassing the compound's broader classification within the kaurane family of

diterpenoids. This name underscores the compound's structural relationship to other members of the kaurane family, facilitating its categorization and comparison within the context of natural product chemistry (Ebi, 2014).

2.5.3 What food and fruit can it be found?

While precise details regarding the specific food and fruit sources of Kaur-16-ol may not be readily accessible in current search results, it is important to acknowledge its classification within the group of diterpenes known as kauranes. As outlined by Mijares *et al*. (2022), kauranes, including Kaur-16-ol, are commonly distributed across a range of botanical sources, including higher plants, lichens, and liverworts. Higher plants, encompassing a diverse array of botanical species, represent a primary reservoir for kauranes. These plants, spanning from flowering plants to gymnosperms, possess intricate biosynthetic pathways capable of producing various secondary metabolites, among which kaurane diterpenes are frequently encountered. While the specific botanical species synthesizing Kaur-16-ol may vary, the prevalence of kaurane diterpenes underscores their importance in plant metabolism and ecology (Mijares *et al*., 2022).

In addition to higher plants, lichens serve as another potential source of kauranes, including Kaur-16-ol. Lichens, symbiotic organisms composed of fungi and photosynthetic partners such as algae or cyanobacteria, thrive in diverse environments worldwide. These unique organisms produce an assortment of bioactive compounds,

including diterpenoids, which contribute to their ecological interactions and adaptation to various habitats (Mijares *et al*., 2022).

Furthermore, liverworts, a group of non-vascular plants belonging to the division Marchantiophyta, represent another reservoir for kaurane diterpenes. Despite their relatively simple morphology, liverworts possess intricate metabolic capabilities, synthesizing a wide range of secondary metabolites, including diterpenoids. The presence of Kaur-16-ol and related compounds in liverworts highlights the chemical diversity and ecological significance of these ancient plants (Mijares *et al*., 2022). While specific information regarding food and fruit sources of Kaur-16-ol may be limited, understanding its distribution across diverse botanical sources sheds light on its ecological role and potential applications in various fields, including pharmacology and natural product research (Mijares *et al*., 2022).

2.5.4 Effects of Kaur-16-ol on Prostaglandin

Although the direct effects of Kaur-16-ol on prostaglandins remain unexplored in available search results, it is intriguing to consider its potential implications, given the documented anti-inflammatory and immunomodulatory properties associated with Kauranes, the class of diterpenes to which Kaur-16-ol belongs (Mijares *et al*., 2022). These findings imply that Kaur-16-ol may possess similar bioactive properties, suggesting a possible role in modulating inflammatory processes and immune responses within the body.

Prostaglandins, as lipid compounds, exert a wide range of physiological effects, including the regulation of inflammation, pain perception, and immune function. While the specific interactions between Kaur-16-ol and prostaglandins have not been elucidated, the anti-inflammatory properties attributed to Kauranes hint at potential mechanisms through which Kaur-16-ol may influence prostaglandin activity (Mijares *et al*., 2022). Inflammation is intricately linked to the production and action of prostaglandins, which play pivotal roles in mediating inflammatory responses and immune signaling pathways.

Given the established anti-inflammatory effects of Kaur-16-ol, it is conceivable that this compound may indirectly modulate prostaglandin synthesis or activity, thereby influencing the inflammatory cascade. By targeting key enzymes involved in prostaglandin biosynthesis or signaling pathways, Kaur-16-ol could potentially attenuate inflammatory processes, offering therapeutic benefits in conditions characterized by excessive inflammation or immune dysregulation (Mijares *et al*., 2022).

Moreover, the immunomodulatory properties associated with Kauranes suggest broader implications for Kaur-16-ol in regulating immune responses beyond inflammation. Prostaglandins play multifaceted roles in immune function, including the regulation of immune cell activation, cytokine production, and immune cell trafficking. While the precise mechanisms underlying these interactions remain to be

elucidated, the potential for Kaur-16-ol to modulate immune responses warrants further investigation (Mijares *et al*., 2022).

(Furtado et al., 2024) investigating the effect of Kaurenol found in copaiba essential oil on the potential anti-inflammatory and antinociceptive properties of kaurenol reported that kaurenol contain in copaiba oil were found to cause the release of Nitric oxide, serotonin and prostaglandin.

2.6 Kaur-16-en:

2.6.1 Description

Kaur-16-en, alternatively known as Kaur-16-ene, represents a notable member of the diterpene class, characterized by its distinct molecular structure and composition (Vieira *et al*., 2002). With a molecular formula of $C_{20}H_{32}$ and an average mass of 272.468 Da, Kaur-16-en embodies the structural complexity typical of diterpenes, consisting of twenty carbon atoms arranged in a specific configuration (Vieira *et al*., 2002). Within the realm of natural products, diterpenes exhibit remarkable diversity in chemical structures and biological activities, contributing to their significance in various fields ranging from pharmacology to ecology.

The structural features of Kaur-16-en render it a member of the broader family of kauranes, which encompasses a diverse array of diterpenoids sharing similar structural motifs (Vieira *et al*., 2002). Kauranes are characterized by the presence of a characteristic bicyclic core structure, typically comprising a fused tetracyclic ring system. This structural arrangement imparts unique physicochemical properties and

biological activities to kaurane diterpenes, rendering them intriguing subjects for scientific investigation and exploration (Vieira *et al*., 2002).

In natural systems, Kaur-16-en is synthesized through the intricate biosynthetic pathways of plants, fungi, and certain microorganisms, reflecting its widespread occurrence in nature (Vieira *et al*., 2002). The biosynthesis of diterpenes involves a series of enzymatic reactions catalyzed by specialized enzymes, leading to the formation of diverse structural variants such as Kaur-16-en. These metabolic pathways play pivotal roles in plant growth, development, and defense, underscoring the ecological significance of diterpenoid metabolism in natural ecosystems (Vieira *et al*., 2002).

Furthermore, Kaur-16-en and related kauranes have garnered significant interest in the fields of pharmacology and drug discovery due to their diverse biological activities (Vieira *et al*., 2002). These bioactive compounds exhibit a wide range of pharmacological properties, including antimicrobial, antiinflammatory, and anticancer activities, among others. The structural diversity within the kaurane family offers ample opportunities for the development of novel therapeutic agents targeting various diseases and disorders (Vieira *et al*., 2002).

2.6.2 Common Name of Kaur-16-en:

In addition to its common name, Kaur-16-en, this compound is recognized by several other names within the scientific literature, reflecting its varied nomenclature and usage across different contexts (Vieira *et al*., 2002). Among these alternate

designations are (-)-Kaur-16-ene, (-)-Kaurene, Ent-Kaur-16-ene, EntKaurene, 16Kaurene, and Kauren-16-ene, each providing insight into different aspects of the compound's structural or chemical properties (Vieira *et al*., 2002). This diversity in nomenclature underscores the compound's significance in various fields, including natural product chemistry, pharmacology, and ecological studies, where it may be encountered under different aliases (Vieira *et al*., 2002).

(-)-Kaur-16-ene, one of the alternative names for Kaur-16-en, highlights the stereochemical configuration of the compound, specifically referring to its chiral nature and the orientation of substituent groups around the molecule's carbon backbone (Vieira *et al*., 2002). Stereochemistry plays a critical role in determining the biological activity and properties of organic compounds, influencing their interactions with biological targets and physiological processes. As such, understanding the stereochemistry of Kaur-16-en is essential for elucidating its pharmacological effects and ecological functions (Vieira *et al*., 2002).

Similarly, the designation Ent-Kaur-16-ene, derived from the term "ent," signifies the compound's entpimarane skeleton, a characteristic structural feature shared by many diterpenoids within the kaurane family (Vieira *et al*., 2002). This nomenclature provides insight into the compound's biosynthetic origin and evolutionary relationships, highlighting its phylogenetic connections to other diterpenes derived from common precursor molecules. By tracing the biosynthetic pathways leading to Ent-Kaur-16-ene, researchers can gain valuable insights into the metabolic processes

and enzymatic transformations underlying its formation in living organisms (Vieira *et al*., 2002).

Furthermore, the term Kauren-16-ene underscores the compound's classification as a member of the kaurane family of diterpenes, denoting its structural resemblance to the archetypal kaurane scaffold characterized by a fused tetracyclic ring system (Vieira *et al*., 2002). Kauranes constitute a diverse group of natural products found in a wide range of plant species, where they serve various biological functions, including defense against herbivores, regulation of growth and development, and modulation of physiological processes. The identification of Kaur-16-en as a kaurene derivative underscores its evolutionary and ecological significance within the broader context of diterpenoid metabolism and plant biochemistry (Vieira *et al*., 2002).

2.6.3 What food and fruit can it be found?

While the precise food and fruit sources containing Kaur-16-en are not explicitly outlined in available literature, it is essential to recognize that Kaur-16-en is a member of the kaurane family of diterpenes, which typically occur in a variety of botanical sources (Mijares *et al*., 2022). Kauranes are commonly distributed across higher plants, lichens, and liverworts, reflecting their widespread occurrence in nature and diverse ecological roles (Mijares *et al*., 2022). Although specific food items may not be identified, the presence of Kaur-16-en in botanical species suggests potential dietary exposure through the consumption of plantderived products.

The prevalence of Kaur-16-en and related kauranes in higher plants underscores their ecological significance and adaptive functions within terrestrial ecosystems (Mijares *et al*., 2022). These compounds often serve as secondary metabolites involved in plant defense mechanisms, mediating interactions with herbivores, pathogens, and environmental stressors (Mijares *et al*., 2022). By synthesizing and accumulating kauranes, plants can deter herbivory, inhibit microbial pathogens, and regulate physiological processes crucial for survival and reproduction. Therefore, the dietary intake of Kaur-16-en may indirectly occur through the consumption of plant-based foods rich in kaurane-containing species.

Moreover, the presence of Kaur-16-en in lichens and liverworts highlights the compound's broader distribution across diverse taxa within the plant kingdom (Mijares *et al*., 2022). Lichens, symbiotic associations between fungi and photosynthetic organisms, often produce an array of specialized metabolites, including diterpenoids like kauranes, which contribute to their ecological success and adaptation to various environmental conditions (Mijares *et al*., 2022). Liverworts, primitive non-vascular plants, also produce a wide range of secondary metabolites, reflecting their evolutionary significance and ecological roles in terrestrial ecosystems. While the direct consumption of lichens and liverworts as food sources may be uncommon, the presence of Kaur-16-en in these organisms suggests potential dietary exposure through indirect routes, such as consumption of lichen-derived products or herbal remedies.

Furthermore, the utilization of kaurane-containing plants in traditional medicine and herbal remedies further underscores the potential for dietary exposure to Kaur-16-en and related compounds (Mijares *et al*., 2022). Many cultures worldwide have a long history of using medicinal plants rich in diterpenoids for various therapeutic purposes, including the treatment of inflammatory conditions, digestive disorders, and respiratory ailments (Mijares *et al*., 2022). While the direct ingestion of plant extracts or decoctions containing Kaur-16-en may not be common in modern dietary practices, the historical and cultural significance of these plants suggests potential avenues for exposure to Kaur-16-en through traditional medicine practices and herbal preparations.

While the specific food and fruit sources of Kaur-16-en may not be readily identifiable, its presence in higher plants, lichens, and liverworts suggests potential dietary exposure through the consumption of plantderived products, traditional medicines, and herbal remedies (Mijares *et al*., 2022).

2.6.4 Effects of Kaur-16-en on Prostaglandin

Although direct evidence linking Kaur-16-en to prostaglandins is currently lacking, the anti-inflammatory and immunomodulatory properties observed in other kauranes suggest a potential role for Kaur-16-en in modulating inflammatory pathways (Mijares *et al*., 2022). Kauranes, as a class of diterpenoids, have demonstrated significant antiinflammatory effects in various experimental models, including inhibition of proinflammatory cytokines, suppression of inflammatory mediators, and

attenuation of immune cell activation (Mijares *et al*., 2022). Given the involvement of prostaglandins in inflammatory processes, it is plausible that Kaur-16-en may exert its antiinflammatory effects through interactions with prostaglandin synthesis or signaling pathways.

The immunomodulatory properties exhibited by kauranes further suggest potential interactions with prostaglandin-mediated immune responses (Mijares *et al*., 2022). Prostaglandins play crucial roles in immune regulation, influencing the activation, differentiation, and function of immune cells involved in both innate and adaptive immune responses (Mijares *et al*., 2022). By modulating prostaglandin production or activity, Kaur-16-en may indirectly influence immune cell function and cytokine production, thereby contributing to its overall immunomodulatory effects. However, the precise mechanisms underlying the immunomodulatory actions of Kaur-16-en remain to be elucidated and warrant further investigation.

Moreover, the potential interactions between Kaur-16-en and prostaglandins may have implications for various physiological processes beyond inflammation and immune regulation (Mijares *et al*., 2022). Prostaglandins are involved in diverse physiological functions, including vascular homeostasis, gastrointestinal integrity, renal function, and reproductive biology (Mijares *et al*., 2022). Any modulation of prostaglandin activity by Kaur-16-en could impact these physiological processes, influencing vascular tone, gastrointestinal motility, renal perfusion, and reproductive function. Therefore, understanding the interplay between Kaur-16-en and prostaglandins is

essential for elucidating its broader pharmacological effects and potential therapeutic applications.

Nevertheless, it is essential to exercise caution in extrapolating the findings from studies on kauranes to Kaur-16-en specifically, as individual compounds within the kaurane class may exhibit distinct pharmacological properties (Mijares *et al*., 2022). While kauranes share structural similarities and certain biological activities, variations in chemical structure can lead to differences in pharmacokinetics, bioavailability, and target specificity (Mijares *et al*., 2022).

2.6.5 Mechanism of Action on Prostaglandin

Kaur-16-en stimulate cyclooxygenase (COX) enzyme which is known to catalyze the conversion of arachidonic acid to prostaglandin. (Smith, 2018). These molecules are part of a broader class of compounds known as paracoids and autacoids, which function as local hormones, have a short half-life, and act near the point of synthesis (Smith, 2018). They are involved in mediating inflammatory and anaphylactic reactions, and in the uterus, they are critical to vascular tone, normal blood clotting, and orchestrating labor and parturition (Smith, 2018).

In the context of the reproductive cycle, prostaglandin synthesis in the endometrium increases significantly during the late secretory phase compared to the proliferative phase (Smith, 2018). This increase in prostaglandin levels, particularly PGF2α and PGE2, is responsible for the vasospasm of the spiral arteries that typically marks the start of menstruation (Smith, 2018).

2.7 Caryophyllene

2.7.1 Description

Caryophyllene, scientifically referred to as (−)-β-caryophyllene or BCP, belongs to the class of natural bicyclic sesquiterpenes, characterized by their diverse biological activities and widespread occurrence in nature (Ghelardini *et al*., 2001). Among its various sources, caryophyllene is notably found as a constituent in numerous essential oils derived from botanical sources such as clove oil, extracted from the stems and flowers of Syzygium aromaticum, commonly known as cloves (Ghelardini *et al*., 2001). Additionally, it is present in essential oils obtained from Cannabis sativa, copaiba, rosemary, black pepper, and hops, contributing to their characteristic aroma and flavor profiles (Ormeño *et al*., 2008; Gobato *et al*., 2015). This sesquiterpene is particularly distinguished by its structural features, including a cyclobutane ring and a trans-double bond within a 9-membered ring, which are relatively rare in natural compounds (Corey *et al*., 1964).

Black pepper, renowned for its distinctive pungent flavor and aroma, owes much of its sensory appeal to the presence of caryophyllene among other volatile compounds (Jirovetz *et al*., 2002). As a major contributor to the aromatic profile of black pepper, caryophyllene plays a significant role in defining the sensory characteristics and culinary utility of this widely used spice. Its presence in black pepper adds not only to its flavor but also to its potential health benefits, as caryophyllene is known to possess

various pharmacological properties that may contribute to human health and wellbeing.

Caryophyllene has garnered significant interest in scientific research due to its pharmacological activities and potential therapeutic applications. Studies have elucidated its diverse biological effects, including antiinflammatory, analgesic, antioxidant, and neuroprotective properties, among others (Ghelardini *et al*., 2001; Ormeño *et al*., 2008; Gobato *et al*., 2015). These pharmacological activities make caryophyllene a promising candidate for the development of novel therapeutics targeting various diseases and health conditions.

The anti-inflammatory properties of caryophyllene are of particular significance, given the role of inflammation in the pathogenesis of numerous chronic diseases, including cardiovascular disorders, neurodegenerative diseases, and metabolic syndromes (Ghelardini *et al*., 2001). Caryophyllene exhibits anti-inflammatory effects by modulating immune responses, suppressing inflammatory mediators, and attenuating oxidative stress, thereby exerting protective effects against tissue damage and disease progression (Ormeño *et al*., 2008). These anti-inflammatory properties highlight the potential of caryophyllene as a natural remedy for mitigating inflammation-related conditions and improving overall health outcomes.

Moreover, the analgesic properties of caryophyllene have been demonstrated in preclinical studies, where it has shown efficacy in alleviating pain through various mechanisms, including modulation of neurotransmitter pathways and inhibition of

pain signaling cascades (Gobato *et al*., 2015). This analgesic activity underscores the potential of caryophyllene as an alternative or adjunct therapy for managing pain associated with various chronic conditions, offering a natural and potentially safer alternative to conventional analgesic drugs.

In addition to its anti-inflammatory and analgesic effects, caryophyllene exhibits antioxidant properties, which play a crucial role in protecting cells and tissues from oxidative damage caused by free radicals and reactive oxygen species (Ormeño *et al*., 2008). By scavenging free radicals and enhancing endogenous antioxidant defense systems, caryophyllene helps maintain cellular homeostasis and mitigate oxidative stress-induced cellular injury, thereby contributing to overall health and longevity.

Furthermore, emerging research suggests that caryophyllene may exert neuroprotective effects, offering potential therapeutic benefits for neurological disorders such as Alzheimer's disease, Parkinson's disease, and stroke (Gobato *et al*., 2015). Its neuroprotective properties are attributed to its ability to modulate neuroinflammatory responses, promote neuronal survival, and enhance synaptic plasticity, thereby preserving cognitive function and neuronal integrity.

2.7.2 Common Name of Caryophyllene

The common name for Caryophyllene is β-Caryophyllene or BCP1 (Ghelardini *et al*., 2001).

2.7.3 Pharmacology of Caryophyllene β-Caryophyllene, often referred to as BCP, is recognized for its unique pharmacological profile, including its interaction with the Cannabinoid receptor type 2 (CB2 receptor) in rats, where it acts as a full agonist (Ceccarelli *et al*., 2020). Studies have demonstrated that β-Caryophyllene exhibits a high binding affinity for CB2 receptors, with a reported Ki value of 155nM in mice (Alberti *et al*., 2017). Notably, its antiinflammatory effects have been attributed to its activity at CB2 receptors, as evidenced by research comparing pain relief in mice with functional CB2 receptors to those without, with the latter group experiencing minimal benefit (Ceccarelli *et al*., 2020). Furthermore, β-Caryophyllene has been found to possess greater cannabinoid activity compared to the ring-opened isomer αcaryophyllene humulene, suggesting its potential to modulate CB2 activity effectively

(Hashiesh *et al*., 2021). When comparing binding affinities, β-Caryophyllene's interaction with CB2 receptors exceeds that of other cannabinoids such as Cannabinol (CBN) and Delta-9-Tetrahydrocannabinol (THC), underscoring its significance in cannabinoid pharmacology (Russo and Marcu, 2017; Bow and Rimoldi, 2016).

Beyond its cannabinoid activity, β-Caryophyllene has been implicated in enhancing cold tolerance at low ambient temperatures, offering potential benefits for various organisms, including wild giant pandas (Zhou *et al*., 2020). Wild giant pandas have been observed rolling in horse manure, which contains βCaryophyllene/caryophyllene oxide, to inhibit transient receptor potential melastatin 8 (TRPM8), a coldactivated ion

channel. This mechanism suggests a novel adaptive strategy to cope with cold environments, highlighting the multifaceted biological roles of β-Caryophyllene beyond its traditional pharmacological effects.

Moreover, β-Caryophyllene holds promise as a therapeutic agent in cancer treatment, particularly in combination with existing chemotherapeutic drugs. In vitro studies on human colorectal adenocarcinoma have demonstrated that while β-Caryophyllene alone may not significantly inhibit cancer cell growth, its combination with Paclitaxel results in a synergistic effect, leading to enhanced cancer cell growth inhibition compared to Paclitaxel alone (Dudai *et al*., 2018).

2.7.4 What food and fruit can it be found?

Caryophyllene, a prominent sesquiterpene, is widely distributed in nature and is found abundantly in various plant sources, including cannabis (Gilbert and DiVerdi, 2018). It is one of the primary terpenes responsible for the distinctive aroma and flavor of cannabis, contributing to its complex sensory profile (Gilbert and DiVerdi, 2018). Additionally, Caryophyllene is prevalent in several culinary herbs and spices, including black pepper, hops, cloves, oregano, basil, and sage, where it contributes to their characteristic scent and taste profiles (Gilbert and DiVerdi, 2018). Its presence in such a diverse range of plant species underscores its ecological importance and suggests potential functional roles beyond its aromatic properties.

In black pepper, Caryophyllene is one of the major volatile compounds responsible for its pungent aroma and flavor (Jirovetz *et al*., 2002). As a constituent of black pepper

essential oil, Caryophyllene contributes to the spice's sensory characteristics, making it a staple ingredient in culinary and gastronomic traditions worldwide (Jirovetz *et al*., 2002). Its distinct odor profile, often described as spicy, woody, and slightly sweet, enhances the overall sensory experience of dishes seasoned with black pepper, highlighting its significance in culinary applications (Jirovetz *et al*., 2002).

Moreover, Caryophyllene's presence in hops, another common ingredient in brewing, contributes to the aromatic complexity of beer (Gilbert and DiVerdi, 2018). Alongside other terpenes and aroma compounds, Caryophyllene imparts unique sensory qualities to hop-derived products, influencing their flavor profiles and enhancing the sensory appeal of various beer styles (Gilbert and DiVerdi, 2018). Its contribution to the aroma and taste of hops highlights its importance in the brewing industry and its role in shaping the sensory characteristics of alcoholic beverages.

Additionally, Caryophyllene is a key component of cloves, a spice derived from the dried flower buds of the Syzygium aromaticum tree (Gilbert and DiVerdi, 2018). Cloves are valued for their intense flavor and aroma, which are attributed to the presence of Caryophyllene and other volatile compounds (Gilbert and DiVerdi, 2018). The distinctive spicy and aromatic profile of cloves makes them a popular ingredient in various culinary applications, including savory dishes, baked goods, and beverages, further emphasizing the significance of Caryophyllene in the sensory landscape of spices.

Furthermore, Caryophyllene is present in several herbs commonly used in cooking, such as oregano, basil, and sage, where it contributes to their characteristic aroma and flavor profiles (Gilbert and DiVerdi, 2018). These herbs are prized for their culinary versatility and are essential ingredients in Mediterranean and international cuisines, imparting distinctively aromatic and savory notes to a wide range of dishes (Gilbert and DiVerdi, 2018). Caryophyllene's presence in these culinary herbs underscores its importance in gastronomy and culinary arts, where it plays a pivotal role in enhancing the sensory experience of food and beverages.

2.7.5 Effects of Caryophyllene on Prostaglandin

While direct evidence linking Caryophyllene to prostaglandin activity is currently lacking, research suggests that its anti-inflammatory properties, mediated through CB2 receptor activity, may indirectly influence prostaglandin production and activity (Ceccarelli *et al*., 2020). Caryophyllene acts as a full agonist of the Cannabinoid receptor type 2 (CB2 receptor), with studies demonstrating its binding affinity and efficacy in modulating CB2 receptor function (Ceccarelli *et al*., 2020). Given the role of prostaglandins in regulating inflammation and immune responses, Caryophyllene's ability to mitigate inflammation via CB2 receptor activation suggests a potential interplay with prostaglandin pathways, although the precise mechanisms remain to be elucidated (Ceccarelli *et al*., 2020).

Prostaglandins, lipid compounds derived from arachidonic acid metabolism, play crucial roles in modulating inflammation, pain perception, and various physiological

processes (Begum *et al*., 2016). As signaling molecules, prostaglandins exert their effects by binding to specific receptors and initiating downstream signaling cascades that regulate immune responses and tissue homeostasis (Begum *et al*., 2016). While Caryophyllene's interaction with CB2 receptors is well-established, its potential impact on prostaglandin biosynthesis or receptor signaling pathways requires further investigation to delineate the extent of its influence on inflammatory processes (Begum *et al*., 2016).

Experimental studies have demonstrated Caryophyllene's anti-inflammatory effects in various models of inflammation and pain, suggesting its therapeutic potential for inflammatory conditions (Ceccarelli *et al*., 2020). By activating CB2 receptors, Caryophyllene inhibits the release of pro-inflammatory mediators and attenuates immune cell activation, thereby reducing tissue inflammation and injury (Ceccarelli *et al*., 2020). While the precise mechanisms underlying Caryophyllene's antiinflammatory action remain incompletely understood, its ability to modulate immune responses implicates potential interactions with prostaglandin pathways, which play pivotal roles in orchestrating inflammatory processes (Ceccarelli *et al*., 2020).

Inflammatory responses mediated by prostaglandins are tightly regulated by a complex network of signaling molecules and cellular interactions (Begum *et al*., 2016). Prostaglandins exert pleiotropic effects on immune cells, endothelial cells, and other target tissues, influencing vasodilation, vascular permeability, and leukocyte

recruitment to sites of inflammation (Begum *et al*., 2016). Given the multifaceted nature of prostaglandin signaling, the potential interplay between Caryophyllene and prostaglandin pathways raises intriguing questions regarding the modulation of inflammatory responses and the development of novel therapeutic strategies for inflammatory diseases (Begum *et al*., 2016).

While preclinical studies have provided valuable insights into Caryophyllene's antiinflammatory properties and its interaction with CB2 receptors, clinical trials are needed to validate its efficacy and safety in human populations (Ceccarelli *et al*., 2020). Moreover, elucidating the molecular mechanisms underlying Caryophyllene's effects on prostaglandin biosynthesis and signaling pathways could offer new avenues for drug discovery and the development of targeted therapies for inflammatory disorders (Ceccarelli *et al*., 2020).

(Chang *et al.,* 2013) investigating the effect of beta-caryophyllene, a natural bicyclic sesquiterpene on cerebral ischemic injury reported that B-caryophyllene inhibited mRNA expression of inducible nitric oxide synthetases, interleukin (IL)-IB, IL-6 and cyclooxygenase 2 in C6 microglial cell and decreased the level of nitric oxides and prostaglandin E2 at 100µm concentration.

2.8 Caryophyllene Oxide

2.8.1 Description

Caryophyllene oxide, a bicyclic sesquiterpene molecule, is an oxidation derivative of β-caryophyllene, a common constituent of many essential oils derived from various medicinal and edible plants (Gyrdymova and Rubtsova, 2021). Its structural complexity and unique functional groups make it a significant component of essential oils, contributing to their therapeutic properties (Gyrdymova and Rubtsova, 2021). Caryophyllene oxide is renowned for its multifaceted pharmacological activities, including insecticidal, antimicrobial, antifungal, analgesic, and antiparasitic properties (Coté *et al*., 2017). Moreover, it exhibits promising anti-cancer effects and can enhance the anti-proliferative efficacy of conventional cytostatic agents, positioning it as a valuable compound in pharmaceutical research and development (Fidyt *et al*., 2016; Hanušová *et al*., 2017; Park *et al*., 2011).

Caryophyllene oxide's insecticidal properties have been widely recognized, making it a valuable tool in pest management and agricultural practices (Coté *et al*., 2017). As a natural insecticide, it demonstrates efficacy against various insect pests, offering an environmentally friendly alternative to synthetic pesticides (Coté *et al*., 2017). Additionally, its antimicrobial and antifungal activities contribute to its utility in controlling microbial pathogens, both in agricultural settings and pharmaceutical formulations (Coté *et al*., 2017).

In addition to its role in pest management and microbial control, Caryophyllene oxide exhibits analgesic properties, suggesting its potential application in pain management and relief (Coté *et al*., 2017). Its ability to alleviate pain may offer new therapeutic options for conditions associated with acute or chronic pain, providing relief to patients and improving their quality of life (Coté *et al*., 2017). Furthermore, its antiparasitic activity highlights its potential in the treatment of parasitic infections, offering new avenues for drug development and combating infectious diseases (Coté *et al*., 2017).

Caryophyllene oxide's anti-cancer properties have attracted considerable attention in cancer research, with studies demonstrating its ability to inhibit cancer cell proliferation, induce apoptosis, and suppress tumor growth (Fidyt *et al*., 2016; Hanušová *et al*., 2017; Park *et al*., 2011). Moreover, it has been shown to enhance the anti-proliferative effects of conventional cytostatic agents, suggesting its potential as an adjunct therapy in cancer treatment regimens (Fidyt *et al*., 2016).

2.8.2 Common Name of Caryophyllene Oxide

The common name for Caryophyllene oxide is 4,5-epoxycaryophyllene (Gyrdymova and Rubtsova, 2021).

2.8.3 What food and fruit can it be found?

Caryophyllene oxide, a bicyclic sesquiterpene oxide, is prevalent in numerous food and spice plants, as well as essential oils, contributing to their aroma and therapeutic

properties (Aldrich, 2023). It is often encountered in culinary herbs like basil and sage, where its presence enhances both the flavor and fragrance of these herbs (Aldrich, 2023). Additionally, Caryophyllene oxide can be found in plants like Syzygium cordatum, commonly known as the water berry tree, which is indigenous to certain regions of Africa and is valued for its medicinal properties (Aldrich, 2023). The widespread occurrence of Caryophyllene oxide in culinary herbs and medicinal plants underscores its importance in both traditional and modern applications. The presence of Caryophyllene oxide in essential oils adds to their therapeutic value and aromatic profile, making them sought-after ingredients in aromatherapy and herbal medicine (Aldrich, 2023). Essential oils derived from plants like basil, salvia, and Syzygium cordatum contain varying concentrations of Caryophyllene oxide, contributing to their diverse pharmacological activities (Aldrich, 2023). These essential oils are commonly used in aromatherapy practices to promote relaxation, alleviate stress, and enhance overall well-being (Aldrich, 2023). Moreover, Caryophyllene oxide's antimicrobial and antifungal properties make essential oils containing this compound valuable in natural skincare and household products (Aldrich, 2023).

In culinary applications, Caryophyllene oxide adds complexity to the flavor profile of dishes, particularly those prepared with herbs and spices rich in this compound (Aldrich, 2023). Basil, for example, is a staple herb in many cuisines worldwide and is prized for its aromatic leaves, which contain Caryophyllene oxide among other

volatile compounds (Aldrich, 2023). The presence of Caryophyllene oxide contributes to basil's distinctive flavor, enhancing dishes ranging from pasta sauces to salads (Aldrich, 2023). Similarly, Caryophyllene oxide found in sage adds depth to savory dishes, while its presence in Syzygium cordatum may impart unique flavor notes to traditional African cuisine (Aldrich, 2023).

Beyond its culinary and aromatic applications, Caryophyllene oxide holds promise in medicinal formulations for its pharmacological properties (Aldrich, 2023). The compound's analgesic, antiinflammatory, and antimicrobial activities make it a valuable ingredient in natural remedies and pharmaceutical preparations (Aldrich, 2023). In traditional medicine, herbs rich in Caryophyllene oxide have been used to alleviate pain, reduce inflammation, and treat various ailments (Aldrich, 2023). Modern research continues to explore the therapeutic potential of Caryophyllene oxide and its derivatives in managing conditions such as arthritis, bacterial infections, and skin disorders (Aldrich, 2023).

While Caryophyllene oxide offers numerous benefits, its concentration and potency may vary depending on the plant source and extraction method (Aldrich, 2023). Therefore, quality control measures are essential to ensure the efficacy and safety of products containing Caryophyllene oxide, particularly those intended for medicinal use (Aldrich, 2023). Additionally, further research is needed to fully elucidate the mechanisms of action and potential drug interactions associated with Caryophyllene oxide, paving the way for its optimized utilization in healthcare and wellness

applications (Aldrich, 2023). Overall, Caryophyllene oxide's presence in food and spice plants, as well as essential oils.

2.8.4 Effects of Caryophyllene Oxide on Prostaglandin

While specific data regarding the impact of Caryophyllene oxide on prostaglandins is currently lacking, research suggests that Caryophyllane sesquiterpenes, a class of compounds that includes Caryophyllene oxide, possess immunomodulatory properties (Gullì *et al*., 2022). Immunomodulation refers to the regulation of the immune system's activity, which can have downstream effects on various physiological processes, including inflammation. Prostaglandins, lipid compounds derived from fatty acids, are known mediators of inflammation, playing crucial roles in both acute and chronic inflammatory responses (Gullì *et al*., 2022). While the precise interaction between Caryophyllene oxide and prostaglandins remains to be elucidated, the immunomodulatory properties of Caryophyllane sesquiterpenes suggest a potential indirect influence on prostaglandin production and activity.

Prostaglandins are lipid signaling molecules that regulate inflammation, pain, and various physiological processes in the body (Gullì *et al*., 2022). They are synthesized from arachidonic acid via the cyclooxygenase (COX) pathway and exert their effects by binding to specific prostaglandin receptors on target cells. Prostaglandins are involved in the initiation and propagation of inflammatory responses, vasodilation, and fever induction, among other functions. Imbalances in prostaglandin production

or signaling can contribute to the pathogenesis of inflammatory diseases, such as arthritis, asthma, and inflammatory bowel disease (Gullì *et al*., 2022).

While Caryophyllene oxide's specific effects on prostaglandins have not been elucidated, its immunomodulatory properties suggest a potential role in modulating inflammatory processes mediated by prostaglandins (Gullì *et al*., 2022). Immunomodulation encompasses a wide range of activities, including the regulation of cytokine production, immune cell proliferation, and inflammatory mediator release. By modulating immune responses, Caryophyllene oxide may indirectly influence prostaglandin synthesis and activity, thereby impacting the inflammatory cascade (Gullì *et al*., 2022).

Preclinical studies have demonstrated the anti-inflammatory effects of Caryophyllene oxide in various experimental models. For example, research has shown that Caryophyllene oxide inhibits the production of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and suppresses the activation of nuclear factor-kappa B (NF-κB), a key regulator of inflammatory gene expression (Gullì *et al*., 2022). These findings suggest that Caryophyllene oxide may attenuate inflammation by targeting upstream signalling pathways involved in prostaglandin synthesis and inflammatory mediator release (Gullì *et al*., 2022). Clinical studies investigating the impact of Caryophyllene oxide on prostaglandin levels and inflammatory markers in human subjects has provided valuable insights into its therapeutic potential in inflammatory disorders (Gullì *et al*., 2022).

Additionally, exploring potential synergistic interactions between Caryophyllene oxide and conventional anti-inflammatory agents, such as nonsteroidal antiinflammatory drugs (NSAIDs), has uncovered novel therapeutic strategies for managing inflammatory conditions (Gullì *et al*., 2022). Overall, while the specific effects of Caryophyllene oxide on prostaglandins require further investigation, its immunomodulatory properties hold promise for the development of novel antiinflammatory therapies.

(Ashour *et al.,* 2009) investigating the effect of caryophyllene oxide contained in Bupleurum marginatum oil on the chemical composition to validate its ethnopharmacological uses reported that caryophyllene oxide contain in Bupleurum marginatum were found to inhibit both prostaglandin E2 production and lipoxygenase activity in an in vitro study.

2.8.5 Mechanism of Action on Prostaglandin

Caryophyllene oxide is a sesquiterpenoid compound known for its anti-inflammatory and analgesic properties. While specific studies on caryophyllene oxide's mechanism of action in inhibiting prostaglandin secretion during the germinal phase are not readily available, we can discuss its general mechanism based on its known biological activities.

Caryophyllene oxide is a selective activator of the cannabinoid receptor type (Jang *et al*., 2020) (CB2-R). Activation of CB2-R has been associated with various anti-inflammatory effects, including the reduction of pro-inflammatory cytokines and

mediators (Gyrdymova and Rubtsova, 2021). This suggests that caryophyllene oxide may inhibit prostaglandin secretion by modulating the immune response through CB2-R activation.

Additionally, caryophyllene oxide has been found to significantly inhibit the activity of the CYP3A enzyme (Gyrdymova and Rubtsova, 2021). While CYP3A is primarily known for its role in drug metabolism, its inhibition could potentially affect the pharmacokinetics of substances involved in inflammation and pain pathways, including prostaglandins. The exact mechanism by which caryophyllene oxide inhibits prostaglandin secretion during the germinal phase would likely involve a combination of these effects.

CHAPTER THREE

MATERIALS AND METHODOLOGY

3.1 Materials

Negro pepper *(Xylopia aethiopica* fruit)

Plastic cages

Weighing balance

Plates for feed and water

Plain bottles

N-hexane

Cotton wool

Latex glove

Mortar and pestle

Light microscope

Centrifuge

Microscope slides

Phosphate Buffer Solution

Syringes

3.2 Plant Material

The dried fruits of the *Xylopia aethiopica* were purchased from a local vendor in New Benin Market, Edo State, Nigeria. The botanical identification and authentication were confirmed in the Department of Plant Biology and biotechnology, University of Benin, Benin City, Nigeria. The fruits were air-dried for two weeks and then grind into powder form

3.3 Preparation of Extract

The pulverized fruit (500g) was extracted with n-hexane in a Soxhlet apparatus at a low temperature, under reduced pressure to produce a brown color oil. This yield 40g extract which was then stored in a refrigerator until when needed.

3.4 Experimental Animals

All experiment was performed with female Wistar rats weighing 140g-160g bought from the animal House at the department of Anatomy, University of Benin, Benin city, Nigeria. The animals were allowed to acclimatize to the laboratory condition (temperature 24- 27°C and 12 h light-dark cycle) for two weeks before commencement of the experiment with access to feed and water ad libitum.

3.5 Experimental design

Sixteen (16) female rats were divided into two phases; Germinal phase (gestation day 0-7) and Embryonic phase (gestation day 7-14) of four equal groups. Group A served as the control . Groups B, C and D, were given 0.25, 0.5 and 1.0 ml/kg oil extract of X. aethiopica, respectively. The oil extract was given orally for seven days with an orogastric tube.

3.6 Mating of Animals

There was careful selection of proven fertile male rats based on previous breeding records and observed mating behavior. The pairing process involved combining two female rats with one selected viable male in designated breeding enclosures. This 2:1 ratio was chosen to strike a balance between efficient resource utilization and minimizing aggressive behavior among the males.

3.7 Pregnancy Detection

The presence of sperm in the vaginal smear or observation of a vaginal plug indicates the occurrence of mating. The day that sperm is detected in the vaginal smear is designated as day 0 of gestation.

3.8 Sample Collection

Uterus samples for biochemical analysis were collected. The different dosages of the extract were administered orally to the respective groups of rats for 7days, 24hours after the last doses were administered. The rats were sacrificed using chloroform anesthesia. The uterus was collected from the animal and homogenated with buffer

solution and then centrifuged for 10minutes at 3000rpm to collect the supernatant using a micropipette into another plain sample bottles which was used for the analysis of the prostaglandin level.

3.9 Statistical Analysis

Results are expressed as Mean± SEM. The difference between the means was determined by one-way Analysis of Variance (ANOVA). P-values less than 0.05 were considered to indicate significant in all statistical tests.

CHAPTER FOUR

RESULTS

4.1 Results on Statistical Analysis

Table 1: Comparing the mean values of prostaglandin following the administration of graded doses of negro pepper in pregnant Wistar rats

	Control	0.25 ml/kg	0.5 ml/kg	1.0 ml/kg	F	P
E	395.76±31.86[a]	612.78±107.45[a]	1494.80±362.36[a]	841.97±343.64a	3.307	0.057
G	3078.66±824.10[b]	570.21±135.49[a]	993.73±139.08ab	1772.62±834.73ab	4.601	0.023

Values are expressed as Mean±SEM, Means with different superscripts are statistically significant at p<0.05

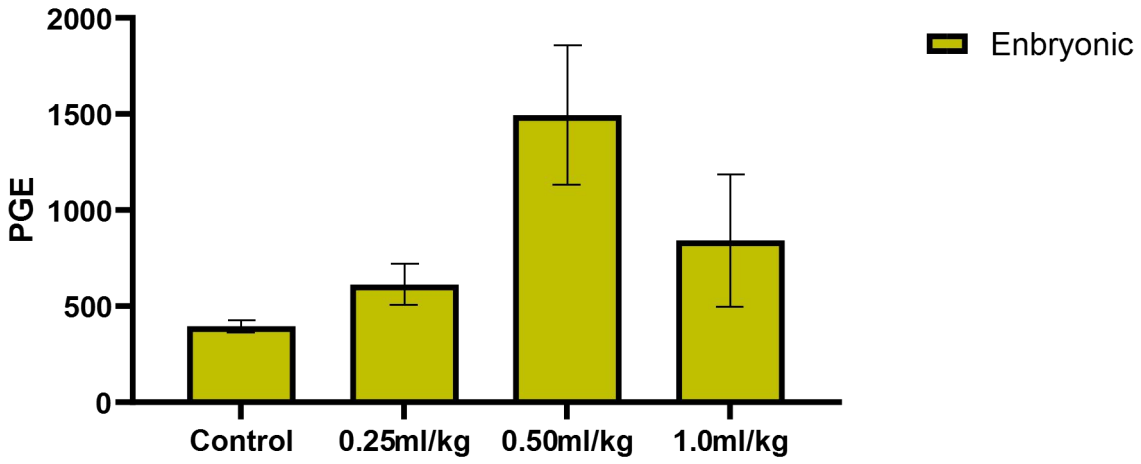


Fig i: Effects of negro pepper extract on Prostaglandin E_2 at embryonic phase of pregnant Wistar rats

There was a significant increase in 0.5ml/kg compared with control, though there were no significant differences in 0.25ml/kg and 1.0ml/kg compared with control

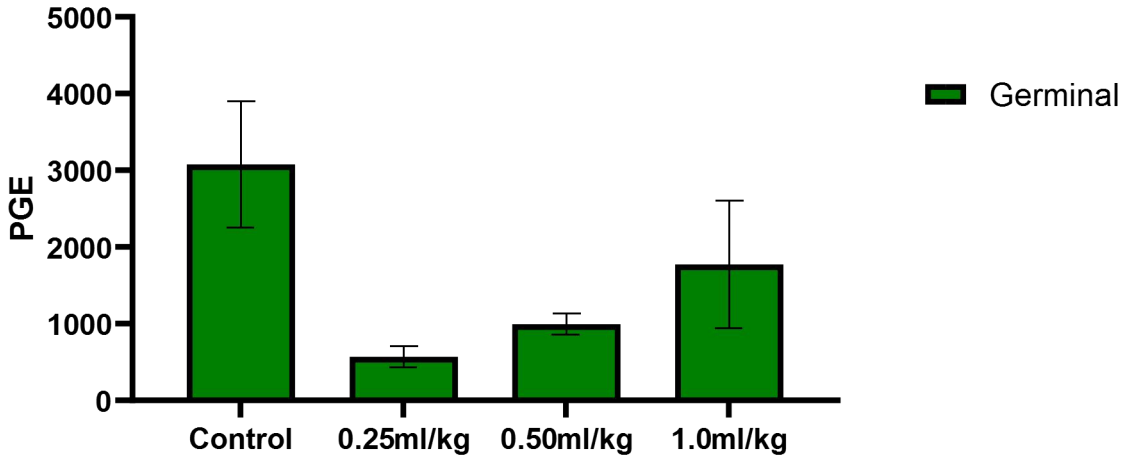


Fig ii: Effects of negro pepper extract on Prostaglandin E_2 at germinal phase of pregnant Wistar rats

There was a significant decrease in 0.25ml/kg, 0.5ml/kg compared with control, though there were no significant differences in and 1.0ml/kg compared with control

CHAPTER FIVE

DISCUSSION AND CONCLUSION

5.1. DISCUSSION

Fig i: Effects of negro pepper extract on Prostaglandin E_2 at embryonic phases of pregnant Wistar rats

There was increase in 1 ml/kg and 0.25 ml/kg but it was not significant compared to control. At 0.5 ml/kg there was significant increase of Prostaglandin E_2.

This result is in line with the study of Furtado *et al*. (2024), who worked on the potential anti-inflammatory and antinociceptive properties of Copaiba oil reported that there was increase in Prostaglandin E_2. The reason for the increase in Prostaglandin level may be as a result of the presence of Kaur-16-ol present in the oil extract of negro pepper.

Kaur-16-ol stimulates Cyclooxygenase (COX) enzyme which is known to catalyse the conversion of arachidonic acid to Prostaglandin.

This result disagrees with the study of Kim *et al* (2013), who reported that there was a decrease in Prostaglandin E_2. In a macrophage cell during an invitro study.

The reason for the decrease in Prostaglandin level may be as a result of the present of

Sabinene present in the oil extract of negro pepper.

Sabinene inhibit COX enzyme which is responsible for producing Prostaglandin.

Fig ii: Effects of negro pepper extract on Prostaglandin E_2 at germinal phases of pregnant Wistar rats

At 1 ml/kg there was decrease but the decrease was not statistically significant compared to control but at 0.25 ml/kg and 0.5 ml/kg there was decrease and the decrease was statistically significant compared to control at the Geminal phase.

This result is in line with the study of Hart *et al*. (2000), who worked on Lipopolysaccharide (LPS) activated human peripheral blood monocyte reported that there was a decrease in Prostaglandin level.

The reason for the decrease may be as a result of the present of Terpinen-4-ol present in the oil extract of negro pepper.

Terpinen-4-ol inhibit COX2 enzyme which is known to catalyse the conversion of arachidonic acid to Prostaglandin level.

This result is also in line with the study of Ashour *et al*, (2009), who worked on the chemical composition, antioxidant, anti-inflammatory, antimicrobial and invitro cytotoxic reported that Caryophellene oxide reduce Prostaglandin E_2 production. The reason for the decrease may be as a result of the presence of Caryophellene oxide present in the oil extra of negro pepper.

Caryophellene oxide inhibits Prostaglandin secretion by modulating the immune responses through cannabinoid receptor.

5.2. CONCLUSION

In conclusion Negro Pepper extract at 0.5 ml/Kg significantly increased PGE_2 level at the embryonic phase but significantly decreased PGE_2 in 0.25ml/Kg and 0.5 ml/Kg in the geminal phase compared to control showing that consumption of negro pepper extract during pregnancy may be detrimental to the pregnancy.

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