The Power of Black Pepper (*Piper nigrum*) in Ayurveda

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ABSTRACT

The field of ayurveda medicine offers potential zero-side-effect remedies to a wide range of issues we often face. Black pepper unquestionably holds a special place in ayurveda medicine, and frequent use can help you reap a host of health advantages. Black pepper (Piper nigrum L.), known as the "King of spices," is a popular spice that gives food its unique flavour while also enhancing the flavour of other ingredients. In-depth research has also been done on the biological characteristics and phytoactive components of Piper nigrum. However, an updated collection of these data is not yet available to give a comprehensive profile of P. nigrum's therapeutic properties. This work aims to conduct a thorough assessment of the scientific literature on the pharmacological qualities, phytochemical makeup, and traditional usage of P. nigrum. Using a combination of keywords, information was found using reputable electronic databases (e.g., Science Direct and Google Scholar). Additionally, Google was used. The literature search was limited to English-language sources, including books and internet content. India had the most historic accounts of P. nigrum in both human and veterinary medicine, particularly for gastrointestinal problems in animals and menstruation and ear-nose-throat illnesses in people. The majority of the ingredients were seeds and fruits, and the main methods of preparation were powder, pills or tablets, and paste. . Additionally, it was discovered that Piper nigrum and its bioactive components possessed significant pharmacological characteristics. Biofilm, bacterial efflux pumps, bacterial swarming, and swimming motilities were all inhibited, which resulted in antimicrobial efficacy against a variety of pathogens. The scavenging of superoxide anion, hydrogen peroxide, nitric oxide, DPPH, ABTS, and its reducing action on ferric and molybdenum are just a few of the reactive oxygen and nitrogen species that studies have shown it to have antioxidant properties against.

Improvement of antioxidant enzymes in vivo has also been reported. Piper nigrum also exhibited anticancer effect against a number of cell lines from breast, colon, cervical, and prostate through different mechanisms including cytotoxicity, apoptosis, autophagy, and interference with signaling pathways. Its antidiabetic property has also been confirmed in vivo as well as hypolipidemic activity as evidenced by decrease in the level of cholesterol, triglycerides, and low-density lipoprotein and increase in high-density lipoprotein. Piper nigrum also has anti-inflammatory, analgesic, anticonvulsant, and neuroprotective effects. The major bioactive compound identified in P.nigrum is piperine although other compounds are also present including piperic acid, piperlonguminine, pellitorine, piperolein B, piperamide, piperettine, and (-)-kusunokinin, which also showed biological potency. As a conclusive remark, P. nigrum should not only be regarded as "King of spices" but can also be considered as part of the kingdom of medicinal agents, comprising a panoply of bioactive compounds with potential nutraceutical and pharmaceutical applications.

I. INTRODUCTION

A flowering vine called black pepper is grown for its dried fruit, which is used as a spice and condiment. Black pepper is a tropical plant that is indigenous to South India and is widely grownthere and worldwide. A perennial woody vine, the pepper plant can reach a height of 4 m when supported by supporting trees, poles, or trellises. Spreading vine that rapidly takes root where trailing stems come into contact with the ground. The leaves are 5-10 cm long, whole, alternating, and 3-6 cm wide. The flowers are tiny and are produced on pendulous spikes that are 4 to 8 cm long at the leaf nodes. As the fruit ripens, the spikes grow to be 7 to 15 cm long. The fruit, known as a peppercorn when dried, is a small drupe five millimetres in diameter, dark red when fully mature,containing a single seed. Dried ground pepper is one of the most common spices in European cuisine and its descendants, having been known and prized since antiquity for both its flavour and its use as a medicine. The spiciness of black pepper is due to the chemical piperine. Pepper loses flavour and its aroma through evaporation, so airtight storage helps preserve its spiciness longer When exposed to light, pepper can lose its flavour, transforming piperine into practically tasteless isochavicine, because pepper aromatics disappear quickly after crushed, most culinary sources advocate grinding whole peppercorns shortly before use. As an alternative to pepper shakers that distribute ground pepper, handheld pepper mills or grinders that manually grind or crush entire peppercorns are employed for this. Since antiquity, dried ground pepper has been used for both flavour and as a traditional remedy.Black pepper is the most traded spice in the world. It is one of the most commonly used spices in cuisines all around the world. Black pepper spiciness is attributed to the chemical piperine, which is not to be mistaken with the capsaicin found in fresh hot peppers.

Black pepper is a common condiment in today's society and is frequently combined with salt. Although pepper mills, forexample, were first discovered in European kitchens in the 14th century, the mortar and pestle method of older times has also been a common practise for centuries. Prior to processing, it has been tried to improve the flavour profile of peppercorns (containing piperine and essential oils) by applying ultraviolet-C light after harvest (UV-C). Piper nigrum (Black pepper) is one of the most widely used

spices and is known as "The King of Spices" due to its international trade. In Urdu and Hindi, it is known as Kali Mirch, Pippali in Sanskrit, Milagu in Tamil, and Peppercorn, White pepper, green pepper, Black pepper, Madagascar pepper in English. Black pepper is used as a preservative, a medicinal ingredient, and in perfumery. There are about 1000 species in the genus Piper, but the most well-known are Piper nigrum, Piper longum, and Piper betli. Black pepper can be used for a variety of applications, including human dietaries, medicine, preservatives, and biocontrol agents. Pepper is used in a variety of sauces and cuisines, including meat dishes, all over the world. It has a significant amount of the potent pharmacologically intriguing alkaloid piperine (1-peperoyl piperidine), which is known to have numerous fascinating effects. According to Tiwari and Singh, when taken orally, this plant and its active ingredient piperine can activate the intestine and pancreas; digestive enzymes while also increasing the release of bile acid from the liver. Black pepper therapeutic properties make it significant. Black pepper can be used medicinally to treat respiratory conditions like cold fever and asthama as well as digestive disorders such large intestine toxins, various gastric issues, diarrhoea, and indigestion. Antihypertensive and anti-platelet, antioxidant, antitumor, antipyretic, analgesic, anti-inflammatory, antidiarrheal, antispasmodic, hepatoprotective, antibacterial, antifungal, anti-thyroids, anti-apoptotic, anti-spermatogenic, insecticidal and larvicidal activities are just a few of the pharmacological properties of piperine. Piperine has been reported to increase the oral bioavailability of several medicines, vaccines, and minerals by blocking various metabolising enzymes. Processed peppercorns are available in a variety of colours, all of which can be utilised in food preparation, particularly common peppercorn sauce.

Black pepper is made from the pepper plant still-green, unripe drupe. The drupes are gently boiled in hot water to clean them and prepare them for drying. Heat causes cell walls in peppers to burst, accelerating the work of browning enzymes during drying. The drupes dry for several days in the sun or by machine, during which time the pepper skin around the seed shrinks and darkens into a thin, wrinkled black covering. When dried, the spice is known as black peppercorn. Some estates separate the berries from the stem by hand and then sun-dry them without boiling. Pepper spirit and oil can be produced from the berries after then peppercorns have been dried. Many medical and cosmetic items contain pepper spirit. Pepper oil is also utilised as an ayurvedic massage oil, as well as in some aesthetic and herbal therapies. White pepper is made entirely of the seed of the ripe fruit of the pepper plant, with the fruit& thin darker-colored skin (flesh) removed. Retting, a method used to do this, involves soaking completely ripe red pepper berries in water for about a week to cause the peppercorn flesh to weaken and degrade. Next, the fruit is removed by rubbing, and the seed is then dried. The seed outer coat may occasionally be removed using different mechanical, chemical, or biological techniques. Commonly used in Chinese, Thai, and Portuguese cuisines is ground white pepper. Because black pepper would obviously stand out, it is occasionally used in various cuisines in salads, light-colored sauces, and mashed potatoes in place of black pepper. White pepper has a distinct flavour overall because it lacks several chemicals found in the drupes outer coat. Like black pepper, green pepper is produced from unripe drupes. The green colour of dried green peppercorns ispreserved by using sulphur dioxide, canning, or freeze-drying. Unripe drupes kept in vinegar or brine are pickled peppercorns, which are also green. Some cuisines, including Thai food and Tamil food, use fresh, unpreserved green pepper drupes. They have been described as "spicy and fresh," with a "bright scent." If not dried or maintained, they deteriorate quickly, making them unsuitable for international shipping. Red peppercorns are often made composed of ripe peppercorn drupes that have been preserved in brine and vinegar. Ripe red peppercorns can be dried using the same color- preserving procedures as green peppercorns. Pink peppercorns are the fruits of the Peruvian pepper tree, Schinus molle, or its relative, the Brazilian pepper tree, Schinus terebinthifolius, both of which are members of a distinct plant family (Anacardiaceae). Because they are part of the cashew family, they may trigger allergic responses, including anaphylaxis, in people who are allergic to treenuts.

II. INDIAN BLACK PEPPER VARIETIES

The pepper cultivars best suited for the environmental factors present in each producing nation's pepper-growing regions have been identified and produced for production. The production and growth characteristics of these cultivars differ. Since these kinds are best suited to the agro-climatic conditions found in each region, it is not advisable to use varieties from other regions as planting material without first proving their compatibility in the proper trials and scientific research. More than 75 different pepper cultivars or types are grown in India. The most well-known of them is Karimunda. In Kerala State, Kottanadan, Narayakodi, Aimpiriyan, Neelamundi, Kuthiravally, Balancotta, and Kalluvally are further significant kinds. In Karnataka State, Billimalligesara, Karimalligesara, Doddigya, Mottakare, and Uddagare are additional significant varieties. Some of these cultivars have been employed in hybridization projects and in the selection of high yielding variants. At the Panniyur Pepper Research Station in Kerala, the first hybrid, Panniyur 1 (Fig. below), was created more than 30 years ago. The pepper producers in India love this hybrid strain. Oleoresin may be extracted effectively using kottanadan. Currently, 12 cultivars, including Panniyur 1, have been made available for cultivation in India by various research facilities located in Kerala's Kozhikode, Panniyur, and Palode.

Figure 1: Indian black pepper varieties

Table 1: Improved pepper varieties in India and their characteristics

Variety	Av. dry yield (kg/ha)	Driage (%)	Quality attributes (%)			Characteristics/ distinguishing features
			Piperine	Oleo-resin	Essential Oil	
Panniyur-1	1242	35.3	5.3	11.8	3.5	Long spikes with large berries, early bearing, performs well in the open. Suitable to all pepper growing areas, except under heavy shade.
Panniyur-2	2570	35.7	6.6	10.9	3.4	Shade tolerant. Suited to all pepper growing areas in Kerala.
Panniyur-3	1953	27.8	5.2	12.7	3.1	Late maturing, performs well in open conditions. Vigorous, suited to all areas in Kerala.
Panniyur-4	1227	34.7	4.4	9.2	2.1	Performs well under adverse conditions including partial shade, a stable yielder suited to all growing areas in Kerala.
Panniyur-5	1098	35.7	5.3	12.3	3.8	Suitable for all pepper growing areas, shade tolerant and good for arecanut gardens, tolerant to nursery disease.
PLD-2	2475	-	3.3	15.5	3.5	Recommended for Trivandrum and Quilon districts of Kerala.
Subhakara	2352	35.5	3.4	12.4	6.0	Suited to all growing areas in Kerala and southern Karnataka. High quality.
Sreekara	2677	35.0	5.1	13.0	7.0	Adapts to varying conditions in all pepper growing areas.
Panchami	2828	34.0	4.7	12.5	3.4	Suitable for all areas of Kerala, except drought prone regions, as it is late maturing.
Pournami	2333	31.0	4.1	13.8	3.4	Tolerant to root-knot nematode. Suited to all regions of Kerala.
Panniyur-6*	2127	33.0	4.9	8.3	1.3	For all regions of Kerala under open cultivation as well as partial shade.
Panniyur-7*	1410	33.6	5.6	10.6	1.5	Vigorous, hardy and a regular bearer. Recommended for Kerala under open conditions and partial shade.

Source: Indian Institute of Spices Research, Kozhikode

III. TAXONOMICAL CLASSIFICATION OF PIPER NIGRUM

Kingdom	**Plantae**
Class	Equisetopsida
Sub class	Magnoliidae
Super order	Magnolianae
Order	Piperales
Family	Piperaceae
Genus	Piper
Species	Nigrum

Figure 2: piper nigrum

CLASSIFICATION DEFINITIONS

Eukaryote: Members of this domain share a few common characteristics. These species' cells have membrane-bound organelles and a functional nucleus. .
Plant: belongs to the Archaeplastida subphylum of eukaryotes. These multicellular animals have celluose as a structural component of their cell walls and chloroplasts, which enable them to engage in photosynthetic activities.
Magnoliophyta ("Angiospermae" or "flowering plants"): The creatures in this subclass of the Kingdom Plantae produce coated seeds, flowers, endosperm, and stamens.
Magnoliopsida ("Dicotyledons, Dicots"): Members of this class develop an embryo with paired cotyledons and have leaves with a structure resembling a net of veins. There are no monocot or eudicot piper plants (true dicotyledon).
PiperalesAn order of dicot flowering plants that includes tiny trees, shrubs, and herbs. Small flowers on the members of this order are arranged in conical formations.
Piperaceae("Pepper" family): Piperales family members typically inhabit warm, tropical, foliated, and shaded habitats.
Piper: Pepper vines are members of a plant genus. The word "long pepper" is derived from the prehistoric Tamil word "pippali." The term "pepper" has been used historically to refer to plants that are equally hot and spicy, leading to the name of common chiles and other plants in the genus Capsicum that are similar to them and contain the hot and spicy chemical capsaicin as "peppers." .
Piper nigrum: Specific species known widely as black pepper which derives its name from the Latin terms for ""pepper" and "black."

IV. BOTANICAL DESCRIPTION

It is a tiny, scented climber that is a member of the Piperaceae family. The plant's roots are woody, wide oval, and have cordate leaves. The creeping, joined, and thickened nodes of the stem. The leaf blades have a wide range in size, are alternating, spreading, and stipule-free. The leaves range in size from 5-7 cm at the bottom to 2-3 cm at the top. The cylindrical flowers have solitary spikes. . The fruits are tiny, ovoid, fleshy spike-like, blunt, oblong, blackish-green, 2.5–3.5 cm long, and 5 mm wide. Long, cylindrical, and oblong describe the adult spikes. The pippali used commercially is made from dried red or black berries with a fragrant scent and flavour. Pippalimula is the name of the root radix. Rhizomatous plants, which can be either terrestrial or epiphytic, are common. Simple or branching stems are both possible. . Simple leaves with whole margins can be alternate, opposite, or whorled in arrangement. They are located at the base of the plant or along the stem. Petioles and stipules are typically present. When crushed, the leaves frequently have a noticeable aromas. Flowers are found in spike-like inflorescences that are either terminal, on the opposite side of the leaves, or in the axils. Each bloom is supported by a peltate bract, and flowers are bisexual without perianth. Anthers have two loci and there are 2–6 hypogynous stamens. A single pistil, which is one or three carpellate pistils, is typically linked to three to four stigmas per flower. One superior loculus makes up the ovary. Fruits resemble drupes and have a solitary seed each. The seeds include a tiny embryo and perisperm that is mealy.

Figure 3: Pepper plant parts

V. NUTRITIONAL VALUE OF BLACK PEPPER

We can call it a 'superfood' as it is a rich source of a large number of nutrients. 4.4 grammes of carbs are found in one tablespoon of black pepper. Less than 1 tablespoon is normally used for cooking. The amount of carbs added to the dish is essentially minimal, and thus would have basically little impact on blood sugar levels. Black pepper has a negligible glycemic index and has no effect on blood sugar because it contains about 2 grammes of fibre per tablespoon. It has a very little amount of protein, no cholesterol, and a negligible amount of fat. Be sure to get protein from a variety of sources. . A good source of several vitamins and minerals is black pepper. It is also a great source of manganese, which is necessary for a healthy metabolism, strong bones, and fast wound healing. Vitamin K, which is important for blood clotting, bone metabolism, and controlling blood calcium levels, is also abundant in black pepper. Black pepper also contains calcium, potassium, vitamin B complex, vitamin E, vitamin A, and vitamin C. Black pepper contains only 17 calories per tablespoon, which is a negligible amount of calories. For an in-depth review of nutrients, see the table below:

Table 2: Nutrient content per 100 grammes. (Source: National Nutrient Database of the USDA)

Principle	Nutrient Value	Percent of RDA
Energy	255 Kcal	13%
Carbohydrates	64.81 g	49%
Protein	10.95 g	19.5%
Total Fat	3.26 g	11%
Cholesterol	0 mg	0%
Dietary Fiber	26.5 g	69%
Vitamins		
Choline	11.3 mg	2%
Folic acid	10 µg	2.5%
Niacin	1.142 mg	7%
Pyridoxine	0.340 mg	26%
Riboflavin	0.240 mg	18%
Thiamin	0.109 mg	9%
Vitamin A	299 IU	10%
Vitamin C	21 mg	35%
Vitamin E	4.56 mg	30%
Vitamin K	163.7 mcg	136%
Electrolytes		
Sodium	44 mg	3%
Potassium	1259 mg	27%
Minerals		
Calcium	437 mg	44%
Copper	1.127 mg	122%
Iron	28.86 mg	360%
Magnesium	194 mg	48.5%
Manganese	5.625 mg	244.5%
Phosphorus	173 mg	25%
Zinc	1.42 mg	13%
Phyto-nutrients		
Carotene-ß	156 µg	--
Carotene-α	0 µg	--
Crypto-xanthin-ß	48 mcg	--
Lutein-zeaxanthin	205 mcg	--
Lycopene	6 mcg	--

VI. GEOGRAPHICAL DISTRIBUTION

This species is indigenous to the Indo-Malayan area. It is primarily grown in regions with considerable rainfall, limestone soil, and high humidity. The majority of the world's tropical countries, including India, Vietnam, Malaysia, Indonesia, China, and Brazil, as well as Sri Lanka and the West Indies on a smaller scale, are currently where this crop is grown. With 163,000 tonnes, or nearly 34% of the global production, of black pepper, Vietnam is the world leader in this industryThe plant is a long-standing cash crop in the nation, and 95% of the black pepper that is produced is exported, mostly to the US, India, the Netherlands, and Germany. With 89,000 tonnes produced, Indonesia comes in second place after India's 53,000 tonnes. Kerala, Karnataka, Konkan, and Tamil Nadu are the top pepper-producing regions in India. Brazil (42,000 tonnes) and China (31,000 tonnes) are other nations on the list.

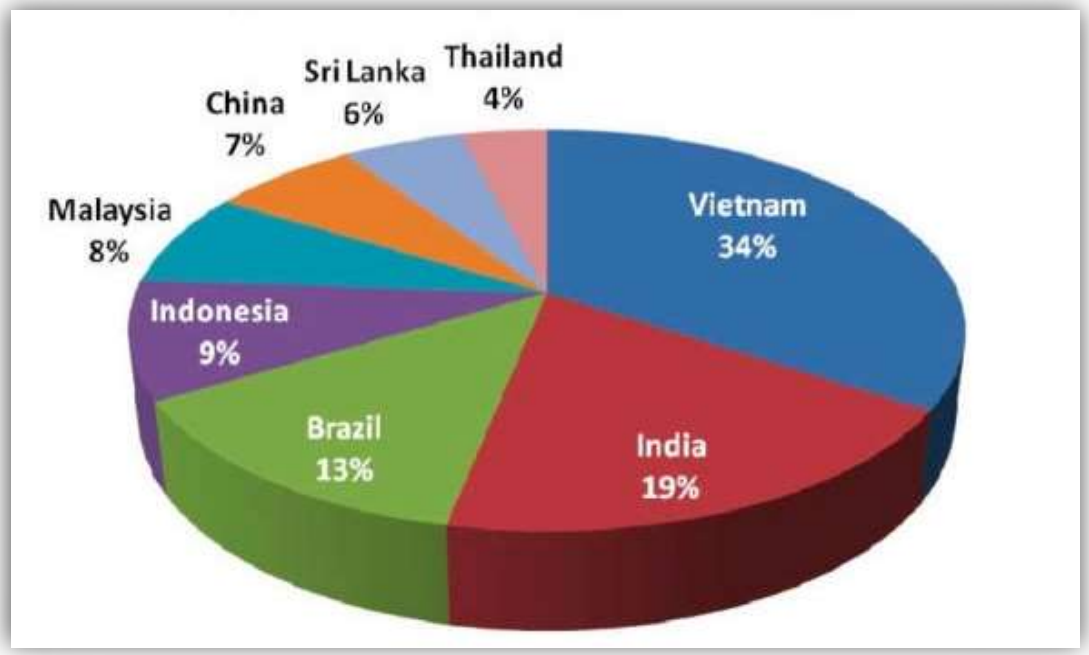

Figure 4: Percentage share of major pepper producing countries

Figure 5: Major Pepper cultivation in India

VII. PHYTOCHEMISTRY OF PEPPER

A. Minerals, vitamins, and biologically active metabolites

Vitamins, minerals, and nutrients abound in black pepper. 100 g of black pepper seeds contain 66.5 g of carbohydrates, 10 g of protein, and 10.2 g of fat. They also contain a comparatively high amount of minerals, including 400 mg of calcium, 235.8–249.8 mg of magnesium, 1200 mg of potassium, and 160 mg of phosphorus, while sodium, iron, and zinc are present in lower amounts. For daily actions of humans, these minerals are necessary components. . In addition, black pepper contains a lot of vitamins, including Vitamins C, B1, B2, and B3. Nine accessions of black pepper produced in Nigeria exhibited tannin levels that ranged from 2.11 to 2.80 mg/100 g. Ashokkumar et al. revealed flavonoids including catechin, quercetin, and myricetin as well as carotenoids like lutein and -carotene were found in considerable concentrations in a recent study on black pepper. .

B. Essential oil, Oleoresin and Piperine

Numerous researchers examined piperine, oleoresin, and essential oils (EO) in various black pepper components. Black pepper leaves and berries have EO yields that range from 0.15 to 0.35 percent and 1.24 to 5.06 percent, respectively. The kind, location, and age of the product, as well as the components and production techniques, all affect the oil yield. In 14 black pepper accessions, Kurian et al. found variation in volatile oil and oleoresin concentration ranging from 2.7 to 5.1 percent and 7.6 to 9.4 percent, respectively. . These researchers noted a good correlation between volatile oil concentration and oleoresin and proposed that the optimum method for enhancing black pepper's quality attributes is to simultaneously improve these traits using a simple selection technique. Classical hydro-distillation was also cited by Kurian et al. as being superior to other approaches for estimating volatile oils. Black pepper's oleoresin concentration ranged from 4.27 to 12.73 percent, and its distinctive natural alkaloid, piperine, ranged from 2.13 to 5.80 percent and 0.12 to 20.86 percent in the seeds and leaves, respectively. Black pepper seeds from south India have an EO profile that is primarily composed of -caryophyllene, followed by limonene, sabinene, -pinene, -bisabolene, -copaene, -cadinol, -thujene, and -humulene; pepper leaves have an EO profiling that is mostly composed of nerolidol, followed by Similarly, EO was found in seeds from Bangladesh, with the highest concentration of EO being -caryophyllene (18.39%), followed by -pinene (16.68%), limonene (16.16%), -pinene (13.61%), -carene (9.23%), -phellandrene (3.16%), copaene (3.13%), -naphthalenol (2.89 percent). Major metabolites in the EO of seeds from Sri Lanka, Malaysia, and Brazil displayed some observable differencesChemDraw software was used to depict the molecular structures of the main constituents of essential oils that were isolated from pepper seeds and leaves. The yield of minor EO of black pepper contained p-Cymene (0.70 percent), Bicyclogermacrene (0.31 percent), Cadinene (0.65 percent), -trans-Bisabolene (1.39 percent), -Elemene (1.74 percent), -Elemene (0.60 percent), -Cubebene (0.99 percent), -Guaiene (0.36 percent), -Zingiberene (0. (0.37 percent), and Germacrene D (0.22 %).

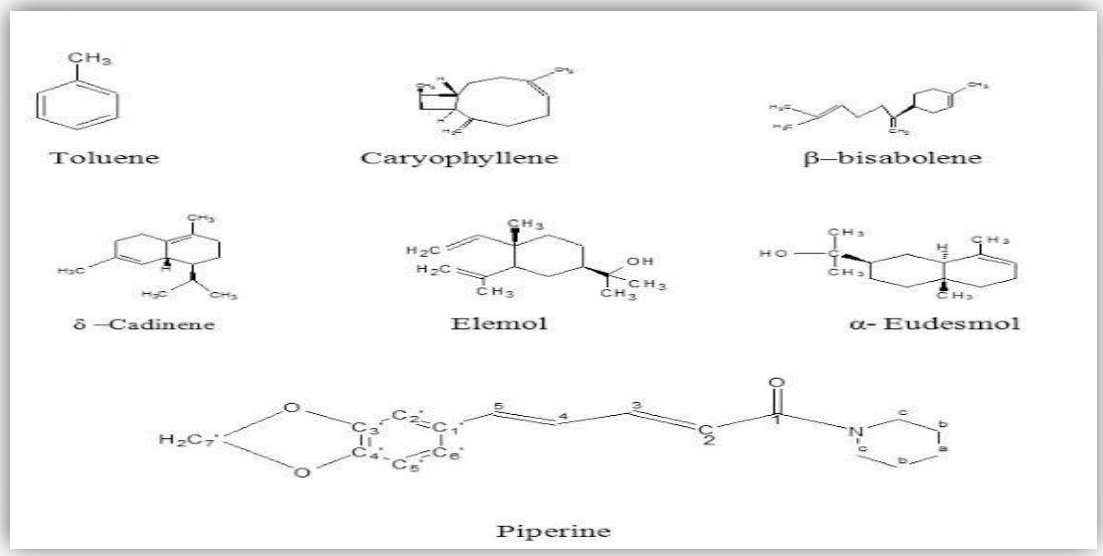

Figure 6: Structure of various components present in pepper plant

VIII. AYURVEDIC HEALTH BENEFITS OF BLACK PEPPER

The ancient ayurveda medical method included pepper as a crucial ingredient. At least 3000 years ago, pepper was used medically in India, according to several records. In the traditional Ayurvedic medical system, pepper played an important role. In the past, it has made it to China. It was being transported overland from India to Sichuan Province by the second century BCE, according to recorded records. Additionally, pepper is mentioned in chronicles of the Han Dynasty (202 BCE–220 CE), which were written in the fifth century CE, as well as in a Tang Dynasty narrative written four centuries later. Pepper was probably originally brought to China from India for medicinal purposes, but it didn't take long for it to start being used as a flavoring agent in food. Due to the discovery of pepper in the nostrils of Ramesses II's mummy, who passed away in 1213 BCE, pepper was also valued in Egypt throughout the New Kingdom (c. 1570–c. 1069 BCE). The Egyptians were sending ships down the Nile to what they called the Land of Punt to acquire exotic goods like frankincense, myrrh, and cinnamon at that time, and little else is known about how they used pepper or the full details of how it got there. However, trade between India and Arabia was already active at that time. .

Black pepper is considered an important healing spice in ayurveda. Along with long pepper and ginger, it forms the herbal preparation called trikatu, an important ingredient in many ayurvedic formulations and it is mentioned in the Charaka Samhita, the ancient Indian guide to a healthy and balanced way of living. The Charaka Samhita is one of two foundational Hindu texts of Ayurvedic teachings that has survived from ancient India. Although pepper is most valued for cooking, its medicinal qualities far outshine its flavor profile. People are increasingly waking up to the health concerns posed by modern medicines and are actively looking for natural remedies. There are numerous issues that we regularly face with possibly fewer adverse effects in the ayurvedic medical field. In ayurvedic medicine, black pepper is unquestionably indispensable, and frequent use can help you reap a host of health advantages. Pepper is a widely utilised, adaptable herb that is frequently recommended for its restorative and balancing properties across India's lengthy Ayurvedic history. Pepper is characterized by Ayurveda as being substantial, slightly greasy, and moisturizing. With a swift and nearly instantaneous action after eating, long pepper is a potent healing plant. Antioxidants are abundant in black pepper. Free radicals are chemicals that are produced both within and outside of our bodies, and these antioxidants help to combat them. Additionally, chemicals, toxins, pollutants, pollution, damaging rays, etc. contribute to free radical formation and damage. Some of these free radicals are also produced naturally from exercise, food digestion, and other processes. Body toxicity and potential serious health issues result from exposure to these free radicals. Black pepper is a beautiful spice with many health advantages. Black pepper is an essential part of traditional Ayurvedic medicine due to its important medicinal benefits as well as its distinctive flavour, which makes it a vital ingredient in many cuisines. Let's examine a few advantages of black pepper according to ayurvedic medical research.

A. Colds and Coughs are Healed by Black Pepper

The most prevalent respiratory issues that we all experience are the average cold and cough. Ayurvedic medications, which have been used for centuries to treat these issues, frequently contain black pepper. These drugs help to clear mucus from the respiratory tract and relieve nasal congestion, which promotes a quicker recovery. Green tea and lukewarm water with turmeric can both be combined with black pepper. Old Ayurvedic treatment for a cold and cough: Black pepper, a pinch of turmeric, and 2-3 drops of honey. Combine well and drink with hot water. In addition to the incredible health benefits of this mixture, black pepper is also known to have immune-boosting properties due to its antibacterial capabilities and gastroprotective modules.

B. Benefits for Your Brain from Pepper

Our brain responds stimulatively to black pepper. Patients with neurological illnesses benefit most from it. By stimulating the chemical pathways in the brain, it helps people's memory and cognitive performance. It also improves mood and functions as an antidepressant. Piperine, a substance found in black pepper, has been demonstrated in animal studies to enhance cognitive function. By causing the brain to produce dopamine, which the disease is brought on by when it isn't there, it has also demonstrated promising outcomes in avoiding Parkinson's disease.

C. Controlling Blood Sugar with Black Pepper

For people with type 2 diabetes, black pepper helps manage blood sugar levels. When the pancreas in our bodies is unable to produce enough insulin or when the body stops responding appropriately to normally normal amounts of insulin, type 2 diabetes develops.
Because of this, dietitians frequently assert that including black pepper in your diet can help reduce the risk of having high blood sugar. Blood sugar levels can be stabilised by black pepper's antioxidant capabilities, which also improve the condition of the digestive system. Additionally, black pepper aids in the battle against obesity, which is one of the main causes of diabetes.

D. Lower Cholesterol Levels with Black Pepper

One of the most prevalent illnesses and the main cause of death in the world is congestive heart failure. The most common causes of this condition are high blood pressure and high cholesterol. According to studies, black pepper may help lower blood cholesterol levels. Black pepper's piperine aids in lowering cholesterol absorption, lowers levels of "bad" cholesterol (LDL, or low-density lipoprotein), and raises levels of "good" cholesterol, or high-density lipoprotein (HDL- High-density lipoprotein). It has been demonstrated that eating black pepper regularly has a beneficial impact on lipid regulation.

E. High in cancer-preventing qualities

Anti-carcinogenic qualities of black pepper have also been demonstrated. With its antioxidant capabilities, the substance piperine helps to prevent tissue damage and minimise cell deterioration. Therefore, due to its anti-inflammatory, antibacterial, and antioxidant properties, ingesting freshly ground black pepper can aid in preventing cancer.

F. The Absorption of Nutrients is Assisted by Pepper

Black pepper helps the body absorb essential nutrients more effectively. Due to its inhibitory impact on drug metabolising enzymes, it can help increase the bioavailability of various minerals, including calcium and selenium, as well as the beneficial components found in green tea and turmeric.

G. Pepper Boosts Digestive Function

Black pepper aids in the digestive process. The entire digestive system has been observed to be stimulated by it. Black pepper contains piperine, which promotes the stomach's production of hydrochloric acid (HCl), another substance that aids in the breakdown of proteins. Additionally, it aids in the treatment of gastrointestinal problems and removes toxins from the intestine. If you are pregnant or using medication, you should see a doctor before adding it to your diet.

H. Pepper Enables Fat Loss

Black pepper aids in the process of losing weight. In addition to aiding in the breakdown of fat cells, it has a big impact on raising body metabolism levels. An enhanced breakdown of lipids is made possible by this higher metabolism. The phytonutrients in its outer layer encourage the breakdown of fat cells and aid in weight loss.

I. Black Pepper Treats Skin Problems

It is well known that black pepper can stop excessive skin pigmentation. A skin disorder called vitiligo causes discoloured patches to form on various parts of the body. It happens when the skin's pigment cells are lost (melanocytes). The pigment melanin, which gives the skin its colour, is produced by these cells. Black pepper keeps the skin's natural colour and helps prevent vitiligo. Black pepper can also assist to clear acne by removing the intoxicants that cause it.

J. Pain relief for arthritis

Black pepper's heat improves blood circulation and lessens joint inflammation in those with arthritis. Additionally, according to Ayurveda, black pepper can aid in your body's removal of uric acid, a major contributor to physical pain.

K. Aids in the treatment of depression

Treatment of depression is one of black pepper's many ayurvedic health advantages. It has the ability to immediately improve memory performance while also having a slowing effect on the indicators of brain ageing. These elements work together to make black pepper a highly effective ayurveda remedy for treating depression.

L. Use of pepper in the treatment of fever and malaria

When treating refractory intermittent fevers, a symptom of malarial infections, black pepper has been shown to be more effective than standard quinine, according to a report by Dr. C. S. Taylor in The British Medical Journal from September 1886. Long pepper was proposed as a potential treatment for chronic malaria at a 1983 symposium in Bombay, India, titled "Therapeutic Approaches to Malaria," sponsored by Ciba Geigy, Ltd. According to reports, long pepper was given to patients who had splenomegaly and persistent malaria (enlarged spleen). Long pepper fruits were administered in doses ranging from 3 to 30, starting with 3 and increasing everyday by 3 fruits. After that, the dosage was lowered from 30 to 3 fruits per day. Drinking long pepper once daily in the early morning involved boiling it in milk and water. According to reports, consuming this concoction stopped the growth of malarial parasites and reduced splenomegaly. Black pepper has been employed in traditional Chinese medicine to treat epilepsy. Chinese researchers recently developed a brand-new antiepileptic medication called Antiepilepserine based on this conventional use. Piperine, the primary alkaloid phytochemical present in members of the Piperaceae family of plants, is chemically related to antiepilepserine. Black pepper has long been utilised as a nerve tonic in Middle Eastern traditional medicine. Piperine's analeptic (nervous system stimulant) characteristics have recently been researched. This study established the efficacy of piperine in preventing morphine-induced respiratory depression in experimental mice.

M. The use of pepper in illnesses of the respiratory system

In Ayurveda and Unani medicine, long pepper and, to a lesser extent, trikatu, have been used to treat asthma and chronic bronchitis. Long-term administration of long pepper fruits dramatically decreased the frequency and severity of the episodes in a trial involving

240 kids of various ages who experienced recurrent asthma attacks. In the trial group, 25 individuals had no recurrence of asthma attacks, 161 showed clinical improvement, 47 showed no response to treatment, and 7 patients' conditions worsened. In a different trial, 20 young asthmatic patients got daily doses of long pepper ranging from 9.35 to 15.75 grammes for several weeks. All of the patients improved clinically as a result of this treatment.

N. Increasing bioavailability by the use of pepper

Traditional remedies for a number of gastrointestinal ailments include the usage of trikatu, long pepper, and black pepper, all of which are thought to help digestion. In the 1920s, Bose, a well-known author of "Pharmacographia Indica," stated that the addition of long pepper to an Ayurvedic formula including vasaka (Adhatoda vasica) improved its antiasthmatic effects. Bose provides instances of his formulation in his "Pharmacopoeia Indica," which includes vasaka leaf juice that has been simmered with sugar, long pepper, and butter before being mixed with honey and administered as a therapy for asthma. Ancient healers found herbal substances, like pepper, via careful trial and observation that might improve the potency of both nutrients and herbal medicines. Trikatu was frequently included in Ayurvedic formulations with the main goal likely being to increase the potency of pharmacologically active substances. The major alkaloid in pepper, piperine, is currently thought to be responsible for this pepper's capacity to increase bioavailability. Piperidine and piperic acid are produced by the hydrolysis of piperine, an alkaloid with the chemical formula C17Hl9O3N, by alkali. l The amount of piperine in pepper directly correlates with how pungent it is. Only recently has piperine's biological characteristics been thoroughly researched. Ancient healers found herbal substances, like pepper, via careful trial and observation that might improve the potency of both nutrients and herbal medicines. Trikatu was frequently included in Ayurvedic formulations with the main goal likely being to increase the potency of pharmacologically active substances. The major alkaloid in pepper, piperine, is currently thought to be responsible for this pepper's capacity to increase bioavailability. Piperidine and piperic acid are produced by the hydrolysis of piperine, an alkaloid with the chemical formula C17Hl9O3N, by alkali. The amount of piperine in pepper directly correlates with how pungent it is. Only recently has piperine's biological characteristics been thoroughly researched. The interaction of piperine with enzymes involved in drug metabolism, like mixed function oxidases found in the liver and intestinal cells, is cited as the explanation for the improved bioavailability of medications when they are taken in conjunction with piperine. Another idea is to interact with the body's natural production of chemicals that help drugs chelate, like glucuronic acid. The metabolism and biodegradation of pharmaceuticals may be slowed by piperine's interactions with oxidative phosphorylation, as well as the activation and deactivation of specific metabolic pathways. Drugs are more readily available for pharmacological activity as a result of piperine's effect, which raises their plasma levels. Atal and colleagues at the Regional Research Laboratory, Jammu-Tawi in India conducted one of the first studies to demonstrate that pepper could increase the bioavailability of medications in the late 1970s. According to these studies, rats that received Piper longum along with the drugs vasicine and sparteine orally had higher blood levels of both substances than control animals that didn't receive P. longum, increasing the blood levels of vasicine by 232 percent and sparteine by more than 100 percent.

Piperine has been shown in later studies to increase the bioavailability of a variety of medications, including rifampicin, phenytoin, propranolol, and theophylline. A patent (Indian Patent No. 1232/DEL/89) based on the drug bioretentive ability of piperine suggests using piperine in combination with medications to increase their efficacy. Since nutritional deficiencies caused by poor gastrointestinal absorption are a growing issue in both developing and Western countries, the successful use of piperine to boost the bioavailability of some medications has sparked interest in the field of nutrient and food absorption. Gross malnutrition as a whole may be to blame in emerging nations. However, due to an increase in the population's proportion of elderly individuals, "junk food diets," allergies, stomach ulcers, and persistent yeast infections, poor gastrointestinal absorption is becoming more common in Western countries (Candidiasis). Human beta-carotene absorption has been found to vary, with some people regularly absorbing it effectively and others not. A recent original bioavailability study demonstrated that a standardised extract of black pepper (Bioperine®) enhances human beta-carotene absorption through the gastrointestinal tract. Piperine, the active ingredient in Bioperine, is 98 percent pure and is extracted from pepper using a specialised method. The blood levels of beta carotene in human volunteers were nearly doubled by the administration of a small dose of Bioperine® (5 mg) along with a recipe containing 15 mg of beta-carotene as a dietary supplement once daily. According to these findings, bioperine may also be able to boost the bioavailability of nutrients. With a dose several times lower than what is typically used to bioenhance blood levels of a medicine, bioperine proved successful in boosting nutritional absorption. Intriguingly, the amount of piperine required to boost beta-bioavailability carotene's was much lower than the daily intake of piperine that a typical person in the USA is thought to eat. Other nutrients including Coenzyme Q1027, L(+) Selenomethionine, Vitamin B6, Vitamin C (with propranolol hydrochloride), and herbal extracts like Curcumin with Bioperine were also found to increase bioavailability in a similar way.

O. The "hot" flavour, "hot" sensation, and thermogenic impact of pepper

Almost everyone is aware that adding black pepper to their food gives it a fiery or "hot" flavour. When pepper is used fresh, the spicy flavour is considerably more potent. The biological action of certain of the phytochemicals included in pepper, most notably piperine, is what gives pepper its heat. Black and long peppers are useful for topical treatment since they excite the skin as well as the tongue. They possess extensive insecticidal, anti-parasitic, and anti-microbial activities. Although peppers have long been employed as local anaesthetics, the mechanism behind their analgesic (pain-relieving) effects has only recently been explained. The primary phytochemical believed to be in charge of pepper's analgesic effects is piperine. The main pungent component of cayenne peppers, capsaicin, is thought to operate similarly to another well-known pungent phytochemical, piperine, but not inexactly (Capsicum annuum). Black and other red peppers, such as cayenne, chilli, and paprika, are all hot but are not botanically related. One theory holds that

piperine may reduce the amount of the neurotransmitter "Substance P" in sensory nerves. Local pain stimuli may become less sensitive as a result of this action. It has been suggested that Bioperine affects the nervous system as a whole and locally in the skin nerve endings through thermoreceptors. In turn, this prevents the transmission of pain stimuli and de-sensitizes pain receptors. The effect of pepper and piperine as thermogenic (heat-generating) agents may be explained by the hypothesised mechanism through thermoreceptors, which are sensors of heat energy in the body. The thermogenic effects of piperine and other spice constituents like capsaicin, gingerol, and shogaol are now widely explored as a novel use for spices that have historically been known for their ability to regulate body temperature. Science has now established a connection between thermogenesis and metabolic rate and body metabolism. The amount of heat energy produced by the body increases with metabolic rate. Could piperine's ability to modulate body temperature be a way to control all aspects of metabolism, including how medications and nutrients are metabolised? Piperine deserves to be referred to as a "super nutrient" since it has such substantial impacts on nutrient absorption when taken orally in doses as low as a few milligrammes, and because of the possibility that it has a thermogenic effect on the body. Ayurvedic medicine did not acknowledge thermogenesis, but it did empirically use certain combinations of minerals and herbs that were intended to increase food digestion. In trikatu (three acrids), a traditional treatment for a variety of gastrointestinal ailments, ginger and black pepper, as well as their near relative long pepper, are combined. Trikatu is a well-established Ayurvedic remedy that has shown to be effective for both acute and chronic gastrointestinal disorders. Its sharp-tasting ingredients are utilised to promote the protective gastrointestinal mucus secretion. Piperine does really possess anti-inflammatory and antioxidant characteristics, according to current experimental research. By reducing inflammatory conditions at the site of absorption, piperine may promote nutrient absorption. Further research is required to determine the processes underlying piperine's positive effects as one of the main components of the many digestive formulae used in Ayurveda. In order to avoid sickness and enhance general nutrition, special emphasis must be focused on the traditional notion of restoring gastrointestinal function. Thus, the herbs long pepper and black pepper have the potential to be helpful in the treatment of a number of respiratory and gastrointestinal issues. Future pepper study may well trace the beginnings and development of the characteristics that drew people to pepper in antiquity. Around 2,000 years ago, Pliny said, "It is somewhat surprising that the usage of pepper has become so popular, considering that its sole attractive quality is a certain pungency; and yet it is for this that we import it all the way from India!" The biological characteristics of piperine, which can reportedly modulate neurohormones and increase thermogenesis—the body's generation of heat—are now known to be the cause of this pungency in pepper. According to recent scientific findings, the taste of "hot" peppers results from the generation of heat energy. Piperine's spicy flavour is closely related to its biological mechanism, supporting the claim that it is a nutraceutical or "functional food."

IX. FORMULATIONS OF PEPPER

It is used in various formulations such as pain balm, relief balm, cough syrups, heart and geri/stress care and joint care balm. Some important formulations include Trikatu, Vardhamanas Pippali rasayana, Talisapatradi churna, pippalyedyesava, kanakasava, balacaturbhadrika, shringyadi churna, amritarishta (amrutharishtam), Gudapippalyadi choorna, shiva gutika, Abhayaristam, Draksaristam, Chayavanaprasam, Pippalyasavam and Kaishore guggulu, Pancakola Curna, Dasamula taila, Dasam ulastapalaka ghrta, Asvagandhadyarista, Amrtariasta, Ayaskrti, Gudapippali.

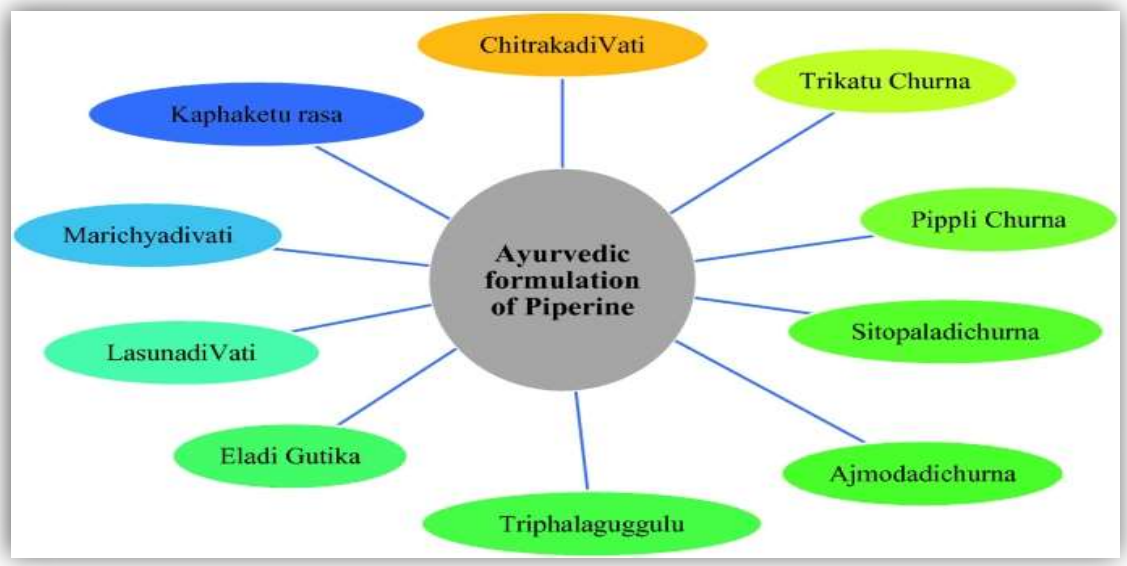

Figure 7: Various formulations of pepper

X. PHARMACOLOGICAL AND BIOLOGICAL EFFECT OF PIPERINE AND BLACK PEPPER ESSENTIAL OIL (BPEO)

The biological effects of the piperine, BPEO, and its constituents include cytotoxicity, anticancer, antibacterial, antioxidant, and other diverse activities.

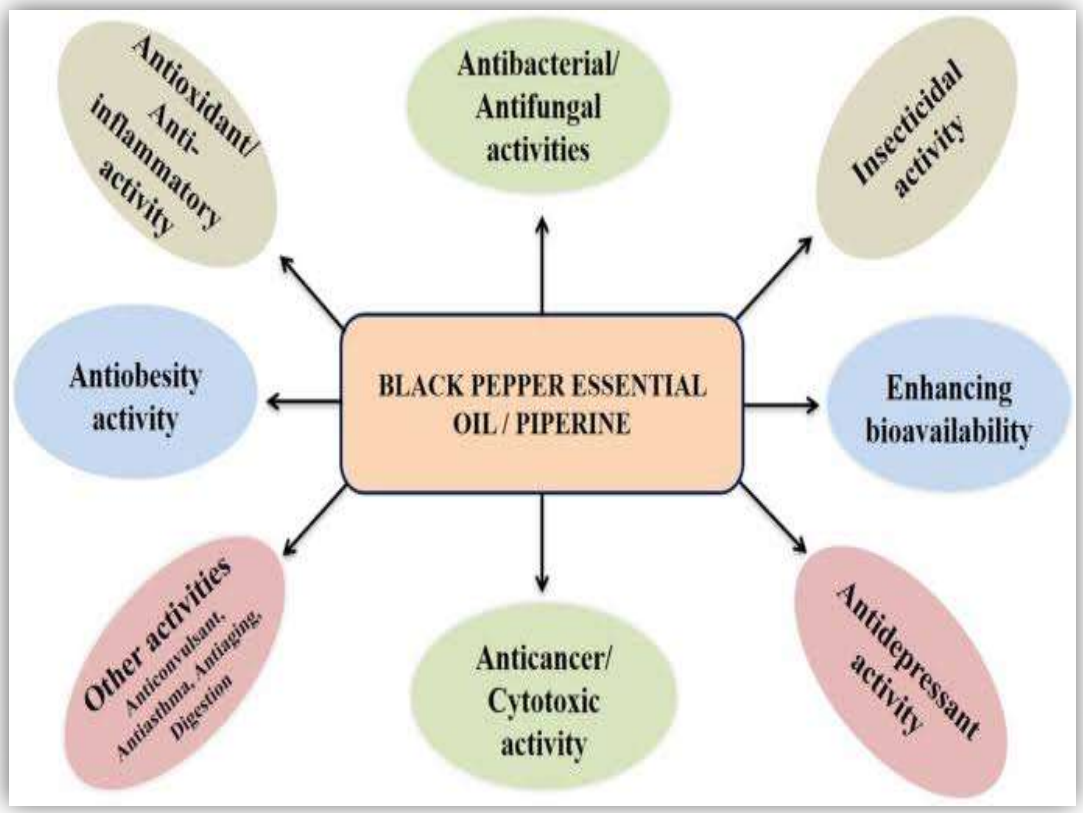

Figure 8: Pharmacological activities of pepper

A substance known as piperine, an alkaloid, is what gives different pepper species their distinctive flavour. In addition to being present in members of the Piperaceae family, it has also been found in a number of other plant species (Rhododendron faurie, Vicoa indica, Anethum sowa, and others). The highest concentration of piperine is found in Piper nigrum L., and it can range from 2 percent to as much as 9 percent, depending on growing conditions and environmental factors like climate and/or origin. The most popular pepper variety is black pepper (Piper nigrum L.), which is also a significant medicinal plant in addition to being used as a spice around the world. Its traditional use dates back thousands of years due to its distinctive function in Ayurvedic medicine, where it serves as one of the "tricatu" components (equal proportions of black pepper, long pepper and ginger). The basis for 210 of the 370 formulations described in the Handbook of Domestic Medicines and Common Ayurvedic Remedies is tricatu or one of its constituent ingredients. Traditional recommendations for pepper include treating neurological and broncho-pulmonary illnesses, as well as a number of gastrointestinal conditions and fevers (asthma and chronic bronchitis). Black pepper is used in traditional medicine, including Chinese medicine, to cure rheumatism, infections like strep throat and influenza, as well as to improve blood circulation and treat a variety of ailments (including headaches and muscle discomfort). In addition to fibre, starch, protein, carbs, and essential oil, pepper also includes lignans, alkaloids, flavonoids, phenols, and amides. Black pepper essential oil, which may be found in the fruits in concentrations of up to 3.5 percent, contains chemicals that give the food its distinctive flavour and scent. Sabinene, -pinene and -pinene, -caryophyllene, phellandrene, limonene, linalool, citral, and other chemicals are the main constituents of this essential oil. Pepper contains a number of different substances, including antioxidants like beta carotene, lauric, myristic, and palmitic acids, as well as piperine. Piperine (piperoylpiperidine), one of pepper's main alkaloids, is responsible for the spice and many of its pharmacological effects. Studies on the physiological effects of piperine have revealed a wide range of effects, including antihypertensive, antiaggregant, antioxidant, anticancer, antispasmodic, antiasthmatic, depressive, anxiolytic, and many more physiological properties. In addition to its wide range of biological functions, piperine is well known for its capacity to raise the bioavailability of medications, hence improving their therapeutic potential. In addition to its advantageous properties, piperine, the major component of the most popular spice, pepper, has been consumed for millennia as food and poses no health risks when consumed. In other investigations, the lack of piperine genotoxicity

in Ames tests and micronucleus tests demonstrated the safety of its consumption. This review includes information from the literature on the various biological effects of piperine as well as the outcomes of human clinical trials.

A. Antioxidant effects

Cancer, immune system problems, diabetes, and Parkinson's disease are just a few of the degenerative and chronic diseases that oxidative stress is a major contributor to the development of. Inhibiting the production of free radicals by scavenging them and suppressing chronic and degenerative diseases are two uses for antioxidants, which can be either natural or manufactured. Hydrogen donation and increased radical stability are benefits of the polyphenolic substance Hydroxytyrosol (HT), which also has strong antioxidant properties. Through the modification of transcription factors NF-B, Nrf2, SREBP-1c, and PPAR- and their target genes, which are involved in inflammation, antioxidant defences, and lipogenesis, supplementation with HT alleviates the white adipose tissue (WAT) dysfunction caused by high-fat diet (HDF) provided to mice. In rats given a high-fat diet that caused oxidative stress to cells, Vijayakumar et al. noted that piperine may have potential protective action against lipid peroxidation and antioxidant activity. With a minimum inhibitory concentration (MIC) of 325 mg/ml or less, piperine was most efficient against all tested gramme positive and negative strains and has the highest antioxidant potential. Jeena et al. found that the essential oil of black pepper reduced tissue lipid peroxidation and scavenged superoxide in vitro.

B. Antibacterial and antimicrobial effects

Customers typically prefer natural and non-toxic products to keep food safe from bacteria while it is being stored. Long-term use of chemical preservatives may lead to a return of food pathogenic bacteria, which can cause serious health issues in people. Black pepper's antibacterial properties are still unknownAgainst Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Aspergillus niger, (A) flavus, Alternaria alternata, and Fusarium oxysporum, piperine may have both antibacterial and antifungal actions. *Bacillus, Escherichia coli, Staphylococcus aureus, S. faecalis, and B. cereus* have the ability to be inhibited by phenolic chemicals found in fresh black pepper seed extracts. According to Zhang et al., black pepper essential oil has the potential to be used as a natural antibacterial agent in the meat business. They demonstrated that 1.0 l/ml of BPEO was the effective minimum inhibitory concentration against meat-borne E. coli. Similar to this, BPEO shown strong efficacy against *S. aureus, B. substilis, and E. coli.*

C. Anticancer effects

The BPEO and piperine have anti-cancer effects on several cancer types. Prostate cancer cells that were both androgen-dependent and androgen-independent experienced a considerable reduction in tumour growth. When piperine and docetaxel were administered together to treat human prostate cancer, Makhov et al. observed increased anticancer activity. Piperine was also a promising therapeutic agent for the treatment of osteosarcoma and caused DNA damage and apoptosis in tumour cells. In a similar manner, piperine decreased lung cancer by promoting antioxidant protection enzymes and by lowering lipid peroxidation. According to the aforementioned remarks, piperine may have anticancer properties. The anticancer potential of piperine and BPEO, however, has only been examined in a few numbers of research, all of which used animal models only. Future research should therefore focus on the bioactivity of BPEO in various clinical tests involving people.

Breast Cancer: According to a study on breast cancer cells overexpressing HER2, activating caspase-3 and cleaving PARP led to an inhibition of proliferation and an induction of apoptosis. Additionally, it was found that piperine increases the susceptibility of HER2 overexpressing cells to paclitaxel death while inhibiting HER2 gene production at the transcriptional level. The same study discovered that it inhibits NF-B and AP-1 activation, blocks the ERK1/2, p38 MAPK, and Akt signalling pathways, and inhibits the expression of MMP-9 that is brought on by epidermal growth factor (EGF). Piperine suppresses the in vitro growth of triple-negative breast cancer cells (TNBC) and hormone-dependent breast cancer cells without affecting the proliferation of normal mammary epithelial cells. Additionally, it enhances the expression of p21(Waf1/Cip1), inhibits the survival-promoting Akt activation, prevents the formation of mammospheres, blocks the Wnt signalling pathway, and inhibits the breast stem cell marker ALDH. All of these effects occur without harming differentiated cells. Another study on TNBC cells found that adding piperine as an adjuvant to factor-related apoptosis-inducing ligand (TRAIL)-based therapy increased its effectiveness. Piperine (35–280 mol/L) injection into tumours in a model of 4T1 murine breast cancer cells slowed the proliferation of 4T1 cells in a time- and dose-dependent manner and reduced the production of MMP-9 and MMP-13. It has been noted that piperine analogues, created by substituting various amino acids and aniline in the piperidine nucleus, exhibit noticeably increased activity against human breast cancer cellsThe greatest cytotoxic action was found in a histidine analogue of piperine with an imidazole ring structure (IC50—0.74 mol).

Lung Cancer: Studies that looked into piperine's impact on lung cancer produced some incredibly encouraging findings. According to Lin et al., piperine induces apoptosis in cancer cells by activating the caspase-3 and caspase-9 cascades, arresting the G2/M phase of the cell cycle, and showing specific cytotoxicity against the lung cancer cell line (A549). Additionally, it raised the Bax/Bcl-2 ratio by increasing Bax protein and decreasing Bcl-2 protein expression. By lowering glutathione transferase (GST), quinone reductase (QR), and UDP-GT and raising the hydrogen peroxide level, benzo(a)pyrene causes lung cancer. Piperine (50 mg/kg b.wt.) and benzo(a)pyrene (BaP) were given orally to mice for 16 weeks in the study on Swiss albino mice. Piperine has been shown to have a protective effect against BaP-induced lung carcinogenesis in mice by reducing levels of lipid peroxidation, protein carbonyls, nucleic acid content, and polyamine production when compared to the control groups. Due to a reduction in GST and UDP-GT, piperine causes BaP-induced

cytotoxicity in V-79 lung fibroblast cells. Piperine administration decreases DNA damage and DNA-protein cross-links in rats with lung cancer. The glutathione-metabolizing enzymes GPx, GR, and glucose-6-phospho dehydrogenase (G6PDH) as well as the mitochondrial enzymes isocitrate dehydrogenase (ICDH), ketoglutarate dehydrogenase (KDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH), and glucos-6-phospho dehydrogenase (G6PD The ATPase enzymes in erythrocyte membrane and tissues were also shown to be upregulated in these animals, while sodium/potassium/magnesium ATPase enzyme activities were downregulated, demonstrating the chemopreventive impact of piperine. Piperine co-administered with tumour induction significantly decreased lung metastasis in C57BL/6 mice (4270 of 29), which was produced by B16F-10 melanoma cells. The findings indicated very promising antimetastatic activity of piperine as evidenced by decreased lung collagen hydroxyproline, uronic acid, and hexosamine content, a significant reduction in tumour nodule formation and lung size, and decreased serum sialic acid and serum -glutamyl transpeptidase activity.

Prostate Cancer: It was discovered that piperine blocks voltage-gated K+ current when it comes to voltage-gated K+ channels (KV), which are thought to be promising targets for the treatment of cancer and play a significant role in regulating cancer cell proliferation. In PC-3 human prostate cancer cells, the IC50 was 49.45 M, whereas in LNCaP, it was 39.91 M. This observed barrier resulted in G0/G1 cell cycle arrest, which in turn prevented cell growth and brought about apoptosis. An additional investigation on human prostate cancer DU145, PC-3, and LNCaP cells demonstrated that piperine likewise caused cell cycle arrest at G0/G1, downregulated cyclin D1 and cyclin A, and elevated levels of p21Cip1 and p27Kip1 after piperine therapy (LNCaP and DU145). Additionally, the elevated level of LC3B-II and the development of LC3B puncta showed that piperine administration enhanced autophagy. Piperine activated caspase-3, cleaved PARP-1 proteins, and decreased the expression of phosphorylated STAT-3 and NF-kB transcription factors in LNCaP, PC-3, and DU-145 prostate cancer cells. According to a recent study, the Akt/mTOR/MMP-9 signalling pathway was the molecular mechanism that caused the observed reduced cell proliferation and migration (in the PCa DU145 cell line) of piperine activity. Ovarian and Cervical Cancer When piperine and mitomycin-C (MMC) were administered together, STAT3/NF-B was inactivated, which suppressed the Bcl-2 signalling pathway in human cervical carcinoma. Additionally, this substance and its analogues showed excellent potential against the Hela cervix cell line. In human ovarian A2780 cells, piperine (8, 16, and 20 M) decreased cell viability and induced apoptosis via the intrinsic apoptotic pathway controlled by JNK/p38 MAPK, according to a recent study. Further investigation into the mechanism of action showed that piperin treatment resulted in higher levels of cyt-c from mitochondria and, as a result, enhanced caspase (caspase-3 and -9) activities as well as decreased phosphorylation of JNK and p38 MAPK.

Cancers of the Gastrointestinal Tract: When hamster buccal pouch cancer was caused by 7,12-dimethylbenz[a]anthracene (DMBA), piperine dramatically raised the levels of lipid peroxidation. FT-IR spectroscopic analysis was used to measure the chemopreventive effectiveness of piperine, and it revealed that treated cancer cells contained fewer proteins and nucleic acids than untreated cancer cells did. Piperine lowers Bcl-2, XIAP (anti-apoptotic), and Akt in AGS human gastric cancer cells while increasing p53, Bax (pro-apoptotic), cleaved caspase-9, and cleaved-PARP. Piperine reduces IL-1-induced IL-6 production in TMK-1 gastric cancer cells via inhibiting IL-1-induced p38 MAPK and STAT3 activation. It also inhibits the growth of HT-29, human colon cancer cells, by lowering the levels of the proteins Bcl-2, Mcl-1, and survivin and raising the levels of the protein Fas. Piperine increases the expression of p21/WAF1 and p27/KIP1 while downregulating the levels of cyclins (D1 and D3), cyclin-dependent kinases (CDK-4 and 6), and cyclins (D1 and D3) in HT-29 colon cancer cells. In the Yaffe et al. investigation, it was discovered that this natural substance prevented the growth of HRT-18 human rectal cancer cells by inducing apoptosis. The same study discovered that the cancer cells treated with piperine produced more reactive oxygen species (ROS), which was at least largely responsible for this effect. The development of colorectal cancer and persistent inflammation have both been linked to the activation of the mTORC1 mechanistic target of rapamycin complex 1. Piperine inhibits TNF- and mTORC1 in human intestinal epithelial cells, acting both alone and in conjunction with curcumin to delay the onset of colorectal cancer.

Other Cancer Types: Piperine decreases NF-B and AP-1 activation, prevents PKC and ERK phosphorylation, and downregulates MMP-9 expression in human fibrosarcoma HT-1080 cells. Piperine (2.5, 5 and 10 g/mL) inhibited the transcription factors NF-B, c-Fos, cAMP response element-binding protein (CREB), and activated transcription factor (ATF-2) from becoming active in B16F10 melanoma cells, which led to a downregulation of the inflammatory and growth regulatory genes IL-1, IL-6, TNF-, and granulocyte-macrophage colony-sti (GM-CSF). Piperine induces cell death in mouse melanoma cells (B16F10) exposed to ultraviolet B via increasing intracellular ROS production, disrupting calcium homeostasis, and reducing mitochondrial membrane potential. Synthetic piperine-amino acid ester conjugates have lethal effects on the human cancer cell lines IMR-32, MCF-7, PC-3, DU-145, Colo-205, and Hep-2.

D. **Cytotoxicity effects**

The efficiency of TNF-related apoptosis in breast cancer cells may be improved with the help of BPEO and piperine. In immune-deficient mice, Greenshields et al. found that piperine and -radiation together had higher cytotoxicity and were more effective at inhibiting the proliferation of tripe-negative cancer cells than radiation alone. The use of cell lines only on in vitro experiments restricts the therapeutically relevance of this result, despite piperine and BPEO's safety having been demonstrated. .

E. **Insecticidal effects**

Black pepper has insecticidal properties that are effective against European chafer (Amphimallon majale, Coleoptera:Scarabaeidae) Black pepper essential oil at a 0.2 percent concentration (v:v) has been found to have possible repellant effect against adults of the main insect that attacks wheat grain storage, Tribolium castaneum, according to Upadhyay and Jaiswal (Herbst). According to Naseem and Khan, a larger quantity of black pepper essential oil produces the most repellent effects at the longest possible exposure times to T. castaneum. Only two studies have examined the insecticidal properties of BPEO thus far; hence, more study is required in this prospective area.

F. Anti-inflammatory effect

An anti-inflammatory is a drug that lessens inflammation in the human body. Black pepper is one of these substances. Inflammation is a complex biological reaction of vascular tissues to damaging stimuli, such as infections, damaged cells, or irritants. About half of analgesics are anti-inflammatory medications, which treat pain by lowering inflammation as opposed to opioids, which act on the central nervous system. Anti-inflammatory medications are frequently used on a long-term basis to effectively manage the compromised immune system for treating chronic inflammatory disorders like rheumatoid arthritis. In IL1-stimulated human FLS, piperine was found to drastically reduce the levels of two key proinflammatory mediators, IL6 and PGE2. Due to PGE2's crucial function in causing pain, its synthesis must be inhibited.As the rate-limiting elements of the collagen breakdown process, MMP1 and MMP13 collagenases also play important roles in RA and osteoarthritis. Because MMP13 destroys a variety of collagenous and non-collagenous extracellular matrix macromolecules and is exceptionally active against collagen type II, the major collagen in cartilage, its considerable reduction of expression is crucial. MMP13 expression is suppressed by piperine in IL1-stimulated FLSs. A carrageenin-induced test including piperine revealed a considerable reduction of the growth of oedema volume. Significant early acute alterations in the inflammatory process were affected by piperine.

G. Antireproductive Activity

According to Srivastava et al., piperine has an antireproductive effect on the snail Lymnaea acuminata. They found that from November 2011 to October 2012, piperine significantly decreased the fecundity, hatchability, and survival of this species. The piperine treatment also delays the snails' time to hatch. After a 96-hour exposure period, sublethal treatment with piperine resulted in a substantial (p0.05) decrease in protein, amino acids, DNA, RNA, and AChE in the ovotestis/nervous tissue of treated snails compared to controls. Additionally, there was a concurrent decrease in acetylcholinesterase (AChE) activity in nerve tissue. Ineffective against L. acuminata is the active ingredient piperine (Piper nigrum). Piperine constituents inhibit the leukotriene and prostaglandin biosynthesis-related enzymes in vitro; COX-1 and 5-lipoxygenase The fresh water pulmonate snail Lymnaea stagnalis has cerebral neurosecretory caudo dorsal cells (CDCS), which regulate egg-laying, a process that involves a pattern of stereotyped behaviour. The ovulation hormone is one of many peptides that the CDCS produce and release (CDCS). It is believed that each peptide regulates a certain aspect of the egg-laying processes.A chemical can influence protein synthesis in any tissue in one of two ways: it can influence RNA synthesis at the transcription stage or it can influence the uptake of amino acids in the polypeptide chain. These two scenarios could explain why the damaged tissue's protein concentration is decreased. In the first scenario, RNA production would be suppressed, resulting in lower protein and RNA content. Only the protein content would change in the second scenario. P-glycoprotein and the key drug metabolising enzyme CYP3A4 are both inhibited by piperine. The level of protein, amino acids, and nucleic acids in L. acuminata's ovotestis appears to be affected by the cumulative effects of the molluscicide piperine either directly or indirectly by DCs, which release ovulation hormone and ultimately have an impact on snail reproduction throughout the year. One of the biomarkers most commonly utilised in ecotoxicology is the AChE activity. The enzyme breaks down ACh in cholinergic synapses, which prevents continuous nerve firing, a necessary component of healthy cellular neurotransmitter activity. As a result of the AChE inhibition, acetylcholinesterase builds up at the nerve synapses, putting the post synaptic membrane in a constant state of stimulation that causes paralysis, ataxia, a general loss of coordination in the neuromuscular system, and ultimately death.

H. Analgesic and anticonvulsant

Researchers are looking into P. nigrum as a potential therapeutic painkiller due to the interest in the search for new, risk-free natural painkillers. We used the tail immersion, analgesy-meter, hot-plate, and acetic acid-induced writhing tests to evaluate the analgesic efficacy of hexane and ethanolic extracts of P. nigrum and its constituent piperine. Piperine's analgesic efficacy peaked in the analgesy-meter test after a dose of 10 mg/kg after 60 minutes, while ethanolextract was most effective after 120 minutes at a dose of 5 mg/kg (reaction time by mice to remove the tail was 11.658 s). In the hot plate method, piperine showed the fastest reaction time for licking or jumping paws (12.870 s after 30 min at a dose of 10 mg/kg). Piperine (10 mg/kg) and the ethanol extract (15 mg/kg) fully halted the number of writhes in mice induced by acetic acid in the writhing test. The impact of P. nigrum as an anticonvulsant was also investigated. Both the pentylenetetrazol (PTZ) induced model and the maximal electroshock seizure (MES) induced paradigm were used by Belemkar, Kumar, and Pata (2013) to determine that the ethyl alcohol and hexane extract of P. nigrum reduced the onset and duration of seizures in Wistar rats. Additionally, Bukhari et al. (2013) discovered that treating mice with 50 mg/kg piperine was more successful than treating them with 70 mg/kg in preventing PTZ-induced seizures. The latency of convulsions caused by picrotoxin increased to 878.5 s at the maximum tested dose of piperine (70 mg/kg), compared to 358.4 s in the control group. both hypolipidemic and hypoglycemic When diabetic rats were given P. nigrum aqueous seed extract for 4 weeks, their blood glucose levels dropped from 270

mg/100 mL to 129 mg/100 mL. (Kaleem, Sheema, Sarmad, and Bano 2005). After 21 days of treatment, diabetic rats given alloxan reduced blood glucose levels by 100, 200, and 300 mg/kg body weight of P. nigrum leaf methanolic extract (Onyesife, Ogugua, and Anaduaka 2014). Aldose reductase is primarily responsible for the onset of long-term diabetic complications because of increased polyol pathway activity; as a result, pharmacological inhibition of this enzyme has been recognised as a key strategy in the prevention and attenuation of related complications, particularly retinopathy, neuropathy, and nephropathy. In fact, the hydromethanolic extract of the seed inhibited goat lens aldose reductase, with an IC50 value of 35.64 lg/mL, according to the research by Gupta, Singh, and Jaggi i2014b. In comparison to rats that did not receive piperine, those on the high fat diet had lower plasma total cholesterol, LDL, VLDL, and HMG CoA reductase levels, while their levels of the enzymes lipoprotein lipase (LPL), lecithin-cholesterol acyltransferase (LCAT), and lipoprotein lipase (LPL) were higher. .

I. Piperine as a repurposing molecule for the reverse of the COVID-19 pandemic

Healthy gut flora helps to increase the immune system of COVID-19 patients. It is necessary to use LC-MS/MS to distinguish between the various microbial metabolites that are produced after piperine and other compounds obtained from plants have been broken down. By changing the expression of genes, microbial metabolites have the capacity to cross the BBB and have pleiotropic effects on the brain and other organs. Fecal Micro-biota Transplantation (FMT) technologies for COVID-19 patients may be a superior method for precision medicine by identifying healthy gut microbiomes in stool samples of COVID-19 patients. In addition to its immune-modulatory effects, black pepper consumption may also directly help fight SARS-CoV-2 through potential antiviral effects. According to a recent investigation, piperine has shown that it can bind to the SARS-CoV-2 spike gly-coprotein and the ACE2 cellular receptor. By generating one predictable hydrogen bond with each amino acid residue, interactions of hydrogen bonds with Gly399, His401, Glu402, Arg514, and Arg518 were determined to be significant. Piperine forms a hydrogen bond with His41 when it interacts with the primary pro-tease, with a docking score of -90.95 and binding energy score of -78.10kcal mol1. Other stabilising interactions include -π -sul-fur, π–σ, π–π T-shaped, and alkyl interactions. Piperine's binding process is additionally controlled by van der Waals interactions with ARG71, TYR121 (TYR453), TYR163 (TYR495), and ASN169 (ASN501) of the SARS-CoV-2 receptor-binding domain spike protein. Piperine has a binding affinity of 6.4 kcalmol-1 (RBD Spro). The main stabilising interactions between piperine and SARS-CoV-2 RBD Spro involved covalent hydrogen bonds, T-shaped interactions, and van der Waals forces. Piperine prevents SARS-CoV-2 replication by interfering with the viral protein Nsp15. Additionally, the intermolecular interactions between piperine and curcumin increase the bioavailability of curcumin, allowing it to bind to the host cell's RBD Spro and ACE-2 receptors and prevent virus entrance.

J. Enzyme-Related Activity

Activity of Monoamine Oxidase By controlling the monoaminergic system, piperine has effects similar to those of antidepressants. The monoamine oxidase (MAO) content is a biochemical indicator of the monoaminergic system, and piperine has been reported to block this enzyme. For the decrease of MAO-A and B by piperine, the IC50 values were 20.9 and 7.0 M, respectively. In addition to piperine, its derivative antiepilepsirine and related compounds methylpiperate, guineensine, and piperlonguminine also had a comparable impact. Piperine displays a synergetic impact on MAO inhibition when combined with ferulic acid. Various Enzymes Cit-P-450, benzphetamine N-demethylase, aminopyrine N-demethylase, and aniline hydroxylase activity are all decreased by piperine. Additionally, piperine decreased TWIK-related spinal cord K+ (TRESK) and acid-sensitive K+ (TASK-1, -3) channel baseline activity in a dose-dependent manner. Its novel anti-epileptogenic target, the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor, is activated, indicating that it has anti-seizure properties. By increasing the ratio of phospho-AKT1 (pAKT1)/AKT1, phospho-AKT2 (pAKT2)/AKT2, and phospho-ERK1/2 (pERK1/2)/ERK1/2 in the testis of rats, piperine enhanced the ratio of phospho-AKT1 (pAKT1)/AKT1, phospho-AKT2 (pAKT2)/AKT2, and phospho-ERK1/2 (pERK1/2)/ERK1/2 in In stressed mice, piperine raises GABA levels and decreases neuronal NOS, resulting in anti-anxiety action. When piperine was administered to animals, P4501A and P4502B expression rose and P4502E1 expression was reduced, according to research on its impact on microsomal P450s. In hepatotoxic rats, acute acetaminophen overdose causes elevated AST and ALT levels. Increased levels of these enzymes are prevented by pretreatment with piperine. Piperine considerably raised GSH levels in the study that examined the free radical scavenging abilities of piperine in a rat intestinal lumen model (exposed to hydrogen peroxide and cumene hydroperoxide). Piperine enhances osteoblast development in MC3T3-E1 cells by decreasing DNA binding-1 and runt-related transcription factor 2 as well as AMPK phosphorylation (Runx2). Piperine blocks cyclooxygenase-2 expression in murine macrophages, NF-B, C/EBP, and c-Jun nuclear translocation produced by phorbol 12-myristate 13-acetate (PMA), inhibits activation of Akt and ERK, and reduces T cell activity and Th2 cytokine secretion in mice with asthma caused by ovalbumin. By increasing caspase 3 and lowering Bax/Bcl 2, piperine displays anticonvulsant efficacy in rats with epilepsy brought on by pilocarpine. In adult male Swiss albino mice, piperine lowers serum concentrations of thyroxin, triiodothyronine, and glucose while lowering the 50D enzyme and glucose-6-phosphatase in the liver. The enzyme activity are comparable to those of propylthiouracil, a common antithyroid medication. Two carbonic anhydrases (CAs), human cytosolic isoforms hCA I and II, are inhibited by piperine. These enzymes are engaged in a variety of physiological and pathological processes, including the development of cancer. They catalyse a physiological reaction in which CO2 is converted to the bicarbonate ion and protons. Its promise as an anti-convulsant, analgesic, anti-tumor, and anti-obesity drug is demonstrated by the discovery of piperine's inhibitory effect against CAs. The enzyme activity was comparable to those of propylthiouracil, a common antithyroid medication. Two carbonic anhydrases (CAs), human cytosolic isoforms hCA I and II, are inhibited by piperine. These enzymes are engaged in a variety of physiological and pathological processes, including the development of cancer. They catalyse a physiological reaction in which CO2 is converted to the bicarbonate ion and protons. Its promise as an anti-convulsant, analgesic, anti-tumor, and anti-obesity drug is demonstrated by the discovery of piperine's inhibitory effect against CAs.

K. Immunomodulatory and Anti-Allergic Effect

Piperine's immunomodulatory properties have shown promising promise. According to Bezerra et al., piperine increased the growth inhibition of 5-fluorouracil (5-FU) when it was incubated with tumour cell lines, as evidenced by reduced 5-FU IC50 values. At the same time, piperine was used in conjunction with 5-FU to diminish leucopoenia, demonstrating better immunocompetence that was inhibited by 5-FU. In the study by Bernardo et al., it was discovered that, in vitro, piperine inhibits the proliferative response induced by lipopolysaccharide (LPS) and immunoglobulin -IgM antibody. This study examined the impact of piperine on B cell functioning and on the humoral immune response to T-un/dependent antigens. Additionally, piperine reduced CD86 cluster of differentiation expression and inhibited IgM antibody production. According to a recent study by Lee et al., piperine and gamma-aminobutyric acid (GABA) together activated p38 and JNK MAPK, increasing the expression of EPO and EPO-R and up-regulating NF-B and IL-10. Piperine demonstrates notable anti-allergic effect in mice with allergic rhinitis brought on by ovalbumin in addition to immunomodulation. However, piperine also reduced nitric oxide (NO) levels due to lower eosinophil migration into nasal epithelial tissue, which in turn decreased nitric oxide (NO) levels and significantly reduced sneezing, rubbing, and redness caused by sensitization of nerve endings caused by histamine released in response to antigen-antibody reaction. As in the histopathological section of the nasal mucosa, it was found that piperine treatment attenuated inflammation, redness, and disruption of alveoli and bronchiole. In an ovalbumin-induced asthma model, the administration of piperine decreased the infiltration of eosinophils and reduced airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production.

L. Neuroprotective and Other Neurological Effects of Piperine

When rotenone causes neurotoxicity in SK-N-SH cells, piperine enhances cell viability and restores mitochondrial function as well as primary neurons. It also has neuroprotective effects in a Parkinson's disease model via inhibiting mTORC1 and activating protein phosphatase 2A. In PC12 Cells and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity, this chemical exhibit protective properties. Piperine also inhibits neurite outgrowth in growing neurons and has neuroprotective effects, particularly on hippocampal neurons in culture. Intraperitoneal injection of piperine (2.5, 5, and 10 mg/kg), vehicle, and memantine (10 mg/kg) for two weeks after the initial STZ administration had cognitive-improving effects in rats with experimental dementia of the Alzheimer's type caused by streptozotocin (STZ). The malondialdehyde levels in the treated rats' cerebrospinal fluid (CSF) and hippocampus (HC) correlated with their cognitive performance. According to the findings, piperine has a positive impact on the redox balance of CSF and HC neurons, which is thought to be the cause of its ability to improve cognition. The injection of piperine decreased oxidative stress and inflammation as well as improved memory impairment in a rat model of epilepsy generated by pilocarpine. In the tail suspension and forced swimming experiments, piperine alone was found to have a negligible antidepressant-like effect; but, when combined with trans-resveratrol (tR), it significantly increased its antidepressive impact. Additional research revealed that the potentiated activation of the brain's monoaminergic system may contribute to the effect of tR and piperine on depressive-like behaviours. Numerous other research on piperine alone, in conjunction with ferulic acid, and its numerous derivatives produced similar results. By modifying the activity of the hypothalamic-pituitary-adrenal axis, piperine alleviates depression in chronic unpredictable moderate stress mice. Piperine was discovered to have analgesic and anticonvulsant properties. When given intraperitoneally (i.p.), doses of piperine of 30, 50, and 70 mg/kg significantly reduced the acetic acid-induced writhing in mice, while doses of 30 and 50 mg/kg caused mice to take longer to react during a tail-flick test. Pentylenetetrazole and picrotoxin-induced seizures in mice were postponed, demonstrating the anticonvulsant effect of piperine. It was discovered that the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors are responsible for piperine's anti-seizure actions. Using the hot plate reaction test and the acetic acid test, a different study showed the analgesic activity of piperine and validated its analgesic efficacy when delivered intraperitoneally.

M. Miscellaneous effects

Black pepper has been used for ages in folk treatments to treat wounds and cuts. By inhibiting P-glycoprotein, piperine increased the bioavailability of the flavonoid linarin in rats and aided cellular efflux during intestinal absorption. Piperine is hence referred to as a natural bio-enhancer. The inhibition of gastrointestinal motility and a dose-dependent increase in stomach acid output are caused by piperine. Piperine taken orally stimulates the small intestinal mucosa's digestive enzymes as well as the liver and pancreas. Additionally, adding piperine to dietary ingredients as a flavouring agent may boost protease, lipase, and pancreatic amylase activity.

Negative Aspects of Piperine: Piperine is acutely poisonous to mice, rats, and hamsters at high dosages. Adult male mice were given piperine intravenously, orally, subcutaneously, orally, and the LD50 values were 15.1, 43, 200, 330, and 400 mg/kg body wt, respectively. The LD50 values for oral administration were determined to be 330 mg/kg for mice and 514 mg/kg for rats. Piperine causes significant liver damage in albino mice by raising aspartate aminotransferase and alkaline phosphatase levels in the blood while lowering total serum protein. Piperine administration improves aflatoxin B1 binding to calf thymus DNA in living tissues in rats. Reduced weights of the caput, corpus, and cauda areas of the epididymis were observed in the D'cruz and Mathur study, which examined the impact of piperine on the epididymal antioxidant system of adult male rats. Additionally, at a dose of 100 mg/kg, the results showed lower sperm count, motility, and viability as well as decreased levels of sialic acid and antioxidant enzyme activity. Therefore, consumption of piperine may impair sperm function because of elevated ROS levels in the epididymis. Recently, piperine (5 and 10 mg/kg) was given to pubertal rats for 30 days, and similar results were noted. In the aforementioned study, piperine improved Leydig cell number and size, testosterone (T) and follicle-stimulating hormone (FSH) levels, but had a detrimental effect on spermatogenesis. The findings of the prior investigation, which treated mature male albino rats with the same therapy (given for 30 days at the same doses

of 5 and 10 mg/kg), indicated solely detrimental effects of piperine to the testes. According to the study's findings, lower doses resulted in partial degeneration of different germ cell types, whereas higher doses resulted in severe damage to the seminiferous tubule, a decrease in caput and cauda epididymal sperm concentrations, a reduction in seminiferous tubular and Leydig cell nuclear diameter, and desquamation of spermatocytes and spermatids. A rise in blood gonadotropins and a decrease in intratesticular T concentration were also noted in these piperine-treated rats.

XI. CONCLUSION

As per the literature study, the P. *nigrum* plant is utilized both as a spice and medicine since ancient times. In Ayurveda medicinal system, there are about 135 ayurvedic formulations where *P. Nigrum* is used as a major ingredient. In the traditional medicinal system, the plant is used to treat numerous diseases such as epilepsy, pleural effusion, spleen disorders, dementia, diarrhea, dysentery, insomnia and many more. There are some reported pharmacological activities of the P. nigrum plant such as antiulcer, anti-inflammatory, anticancer, neuroprotective and others. Still, the plant needs more attention from researchers as the data on the pharmacological properties of this plant is not much explored. This plant claims to treat various diseases as per the literature study but there are no reported pieces of evidence available that showed its effective results. In order to demonstrate the plant's significant effects in treating various diseases, more experimental and clinical studies are required to examine the mechanism of action of plant extracts in the animal body.

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