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. The "King of spices," black pepper (Piper nigrum L.), 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. Both in human and veterinary medicine, India had the longest history of P. nigrum cases., 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. Studies have demonstrated that it has antioxidant capabilities against a variety of reactive oxygen and nitrogen species, including the scavenging of superoxide anion, hydrogen peroxide, nitric oxide, DPPH, and ABTS. It also has a lowering effect on ferric and molybdenum.

It has also been found that antioxidant enzymes can be improved in vivo. Piper nigrum also showed anticancer activity against a variety of cell lines from the breast, colon, cervical, and prostate by several mechanisms such as cytotoxicity, apoptosis, autophagy, and signalling pathway interference. Its anti-diabetic efficacy has also been confirmed in vivo, as has its hypolipidemic activity, as evidenced by a drop in cholesterol, triglycerides, and low-density lipoprotein levels and an increase in high-density lipoprotein. Piper nigrum has anti-inflammatory, analgesic, anticonvulsant, and neuroprotective properties as well. Piperine is the most abundant bioactive ingredient found in P.nigrum, however other substances such as piperic acid, piperlonguminine, pellitorine, piperolein B, piperamide, piperettine, and (-)-kusunokinin were also discovered. As a final note, P. nigrum is not only the "King of Spices," but also a member of the kingdom of medicinal agents, containing a plethora of bioactive chemicals with potential nutraceutical and pharmaceutical applications.

Keywords: Black pepper, piperine, phytochemistry, anticancer activity, antioxidant activity, ancient ayurveda

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. The pepper plant is a woody perennial vine that, when supported by trees, poles, or trellises, can grow as high as 4 metres. Where the earth meets the trailing stems, a spreading vine quickly establishes itself. The leaves are alternate, entire, and 5–10 cm long by 3-6 cm broad. At the leaf nodes, small flowers are produced on pendulous spikes that range in length from 4 to 8 cm. The spikes lengthen to 7 to 15 cm when the fruit ripens. The dried fruit, known as a peppercorn, is a tiny drupe around five millimetres in diameter that becomes a deep shade of red when fully developed and contains just one seed. Dried ground pepper is one of the most common spices in European cuisine and its successors, having been known and cherished since antiquity for both its flavour and its medicinal properties. The chemical piperine is responsible for the spiciness of black pepper. 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. Handheld pepper mills or grinders are used to manually grind or crush whole peppercorns instead of pepper shakers, which disperse ground pepper. Dried ground pepper has been used as a folk cure and flavouring since ancient times. The most traded spice worldwide is black pepper. One of the most often used spices in international cuisines. The chemical piperine, which should not be confused with the capsaicin present in fresh hot peppers, is responsible for the spice in black pepper.

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). Due to its international trade, Piper nigrum (black pepper), one of the most popular spices, is referred to as "The King of Spices." It is also referred to as Kali Mirch in Urdu and Hindi, Pippali in Sanskrit, Milagu in Tamil, and Peppercorn, White Pepper, Green Pepper, Black Pepper, and Madagascar Pepper in English. Black pepper is employed as fragrance, as a preservative, and as a medicine. The Piper genus contains over 1000 species, but Piper nigrum, Piper longum, and Piper betli are the most well-known. Numerous uses for black pepper exist, including as in human dietaries, medicine, preservatives, and biocontrol agents. All around the world, pepper is utilised in a wide range of sauces and cuisines, including meat meals. It contains a sizable amount of piperine (1-peperoyl piperidine), a powerful alkaloid with unique pharmacological properties that is known to cause a variety of fascinating effects. Tiwari and Singh claim that this plant's active element, piperine, can stimulate the intestine and pancreas' digestive enzymes while also boosting the liver's production of bile acid when consumed orally. It is important because of the medicinal characteristics of black pepper. Black pepper can be used as medicine to treat digestive problems such large intestine toxins, different gastric problems, diarrhoea, and indigestion as well as respiratory illnesses like cold fever and asthama.. 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. By inhibiting several metabolising enzymes, piperine has been shown to boost the oral bioavailability of certain medications, vaccines, and minerals. The various hues of processed peppercorns, especially common peppercorn sauce, can be used in food preparation.

The unripe, still-green drupe of the pepper plant is used to make black pepper. The drupes are cleaned and made ready for drying by gently cooking them in hot water. Heat causes the cell walls of peppers to rupture, which enhances the activity of browning enzymes during drying. The pepper skin around the seed shrinks and darkens into a thin, wrinkled black covering when the drupes dry for several days in the sun or with a machine. The spice is called black peppercorn when it is dried. Some estates manually separate the berries from the stem before drying them in the sun. After the peppercorns have been dried, the berries can be used to make pepper spirit and oil. Numerous pharmaceuticals and cosmetics contain pepper spirit. Along with being used in several herbal and aesthetic treatments, pepper oil is also used as a massage oil in ayurveda. The only component of white pepper that remains after the thin, darker-colored skin (flesh) of the pepper fruit is removed is the seed. This is done through retting, which includes soaking fully mature red pepper berries in water for roughly a week to weaken and deteriorate the peppercorn flesh. The fruit is then rubbed off, and the seed is dried after that. Occasionally, the seed's outer covering can be removed by various mechanical, chemical, or biological methods. Ground white pepper is frequently used in Chinese, Thai, and Portuguese cuisines. Black pepper would immediately stand out, so it is occasionally substituted in mashed potatoes, light-colored sauces, and salads across a variety of cuisines. White pepper lacks a number of compounds that are present in the drupe's outer layer, giving it a unique flavour overall. Green pepper is also made from unripe drupes, much like black pepper. Sulfur dioxide, canning, or freeze-drying are three methods used to maintain the green colour of dried green peppercorns. Pickled peppercorns, which are also green, are unripe drupes preserved in vinegar or brine. Fresh, unpreserved green pepper drupes are used in several cuisines, such as Thai and Tamil food. They have been described as having a wonderful scent and being peppery and fresh. If not dried or maintained, they quickly degrade, making them unfit for international shipping. Red peppercorns are usually made from peppercorn drupes that have been preserved in vinegar and brine until they are ripe. The same techniques used to preserve the colour of green peppercorns can also be used to dry ripe red peppercorns. Pink peppercorns are the fruits of the Brazilian pepper tree, Schinus terebinthifolius, or the Peruvian pepper tree, Schinus molle, both of which belong to a different plant family (Anacardiaceae). Being a part of the cashew family, they have the potential to trigger severe responses in people who are allergic to treenuts, including anaphylaxis.

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: This domain's members share a few common characteristics. These species' cells have membrane-bound organelles and a functional nucleus. .
Plant: Belongs to the eukaryotic Archaeplastida subphylum. Celluose is a structural component of the cell walls and chloroplasts of these multicellular organisms, allowing them to perform 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 gets 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 industry .The 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 tonnesTamilnadu, Kerala, Karnataka, and Konkan are the top pepper-producing regions in India. Brazil (42,000 tonnes) and China (31,000 tonnes) are other nations on the list.

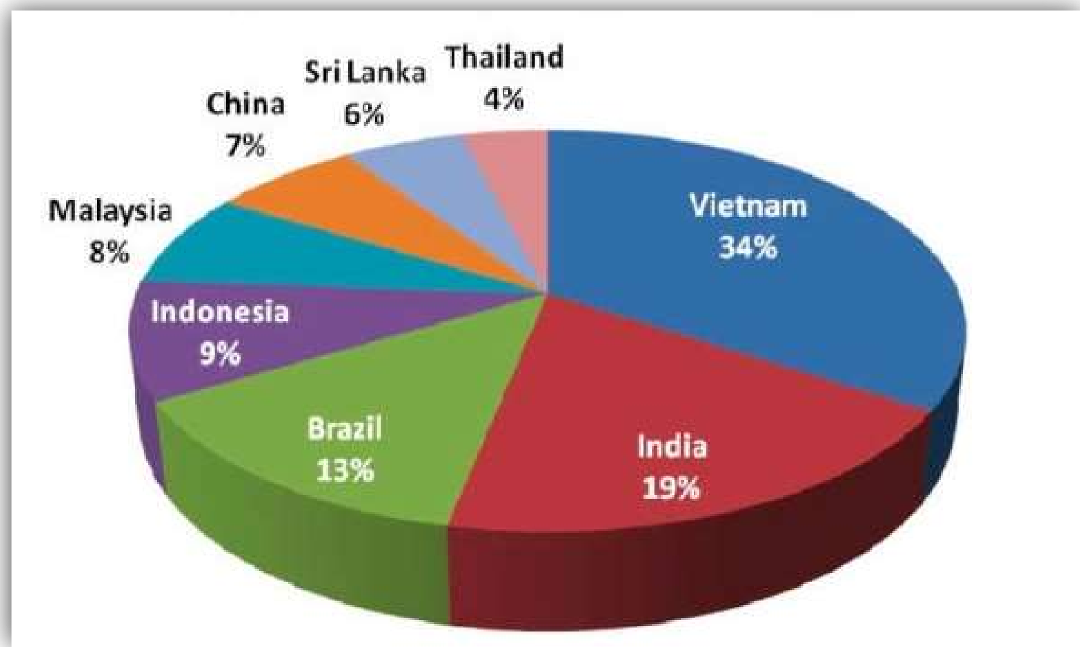

Figure 4: Percentage share of major pepper producing countries

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 %).

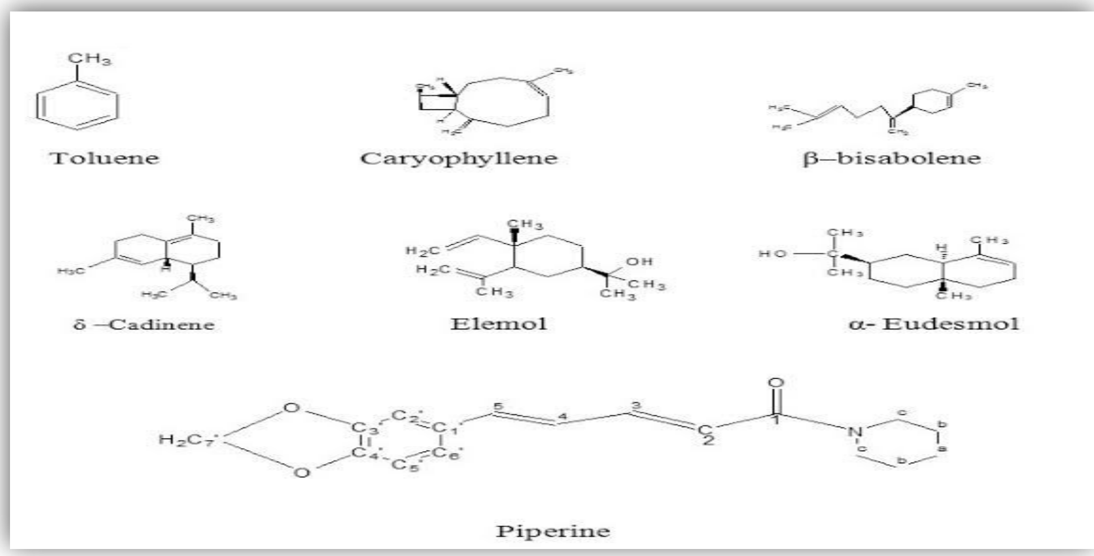

Figure 6: Structure of various components present in pepper plant

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.

In ayurveda, black pepper is revered as a potent therapeutic spice. It is referenced in the Charaka Samhita, an ancient Indian manual on a balanced and healthy way of life, along with long pepper and ginger, which together make up the herbal combination known as trikatu. One of the two primary Hindu books from ancient India that contain Ayurvedic principles is the Charaka Samhita. The medical benefits of pepper considerably outweigh its flavour profile, despite the fact that it is most commonly used in cooking. People are actively seeking out natural cures as they become more aware of the health risks mainstream medications entail. 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. Pepper is a beautiful spice with lots of 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. Treatment of malaria and fever with pepper

According to a research by Dr. C. S. Taylor published in The British Medical Journal in September 1886, black pepper has been demonstrated to be more successful than ordinary quinine in treating refractory intermittent fevers, a sign of malarial infections. At a 1983 symposium in Bombay, India, titled "Therapeutic Approaches to Malaria," sponsored by Ciba Geigy, Ltd., long pepper was suggested as a potential treatment for chronic malaria. Long pepper was reportedly administered to individuals with splenomegaly and chronic malaria (enlarged spleen). Three long pepper fruits were given in doses ranging from three to thirty, with each dose rising by three fruits daily. The dosage was then reduced from 30 to 3 fruits each day. Long pepper was boiled in milk and water and consumed once a day in the early morning. According to accounts, ingesting this mixture slowed the growth of malarial parasites and decreased splenomegaly. Chinese traditional medicine has used black pepper to treat epilepsy. Based on this customary use, Chinese researchers have created a brand-new antiepileptic drug called Antiepilepserine. Antiepilepserine shares chemical similarities with piperine, the main alkaloid phytochemical found in plants belonging to the Piperaceae family. Traditional Middle Eastern medicine has traditionally used black pepper as a nerve booster. Recent studies have focused on the analeptic (nervous system stimulant) properties of piperine. This study demonstrated the effectiveness of piperine in reducing morphine-induced respiratory depression in experimental mice.

M. The application of pepper in respiratory diseases

Long pepper and, to a lesser extent, trikatu have been used to treat asthma and chronic bronchitis in Ayurveda and Unani medicine. In a research involving 240 children of various ages who suffered from repeated asthma attacks, long pepper fruits given over an extended period of time significantly reduced the frequency and severity of the episodes. 25 people in the experimental group experienced no further asthma attacks, 161 experienced clinical improvement, 47 did not respond to treatment, and 7 patients' health deteriorated. In a different study, long pepper was given daily in doses ranging from 9.35 to 15.75 grammes to 20 juvenile asthmatic patients for a period of time. Clinical outcomes for each patient improved as a result of this therapy.

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.

Recent studies have demonstrated that piperine increases the bioavailability of a number of drugs, including rifampicin, phenytoin, propranolol, and theophylline. Based on piperine's ability to retain drugs, a patent (Indian Patent No. 1232/DEL/89) proposes combining piperine with pharmaceuticals to boost their effectiveness. The successful use of piperine to increase the bioavailability of several drugs has aroused interest in the field of nutrient and food absorption since nutritional deficiencies brought on by inadequate gastrointestinal absorption are a rising problem in both developing and Western countries. Overall severe malnutrition may be to blame in developing countries. However, poor gastrointestinal absorption is growing more prevalent in Western nations as a result of a rise in the proportion of elderly people in the population, "junk food diets," allergies, stomach ulcers, and persistent yeast infections (Candidiasis). It has been discovered that human beta-carotene absorption varies, with some individuals consistently absorbing it successfully and others not. According to a new original bioavailability study, the gastrointestinal tract can better absorb human beta-carotene when it is taken as a standardised extract of black pepper (Bioperine). Bioperine's key ingredient, piperine, is purified to 98 percent utilising a specialised process after being taken from pepper. The administration of a tiny dose of Bioperine (5 mg) together with a recipe containing 15 mg of beta-carotene as a food supplement once daily virtually increased the blood levels of beta carotene in human volunteers. These results suggest that bioperine may also increase the bioavailability of nutrients. Bioperine demonstrated efficacy in enhancing nutritional absorption at doses several times lower than those generally used to bioenhance blood levels of a drug. It's interesting to note that the amount of piperine needed to increase beta-bioavailability carotenes was far lower than the amount of piperine a typical American is expected to consume daily.. 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.

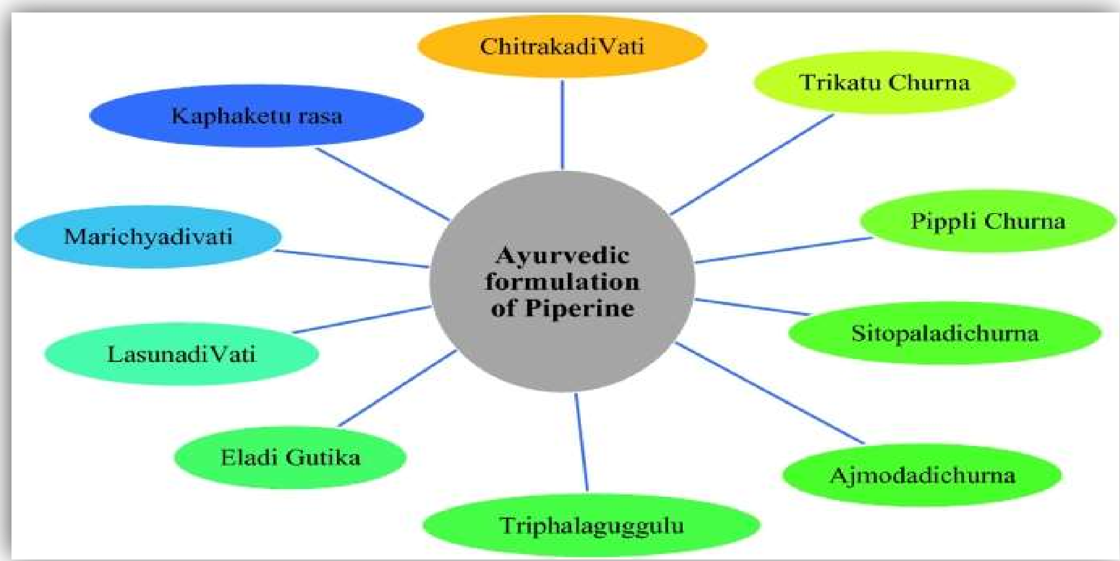

Figure 7: Various formulations of pepper

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.

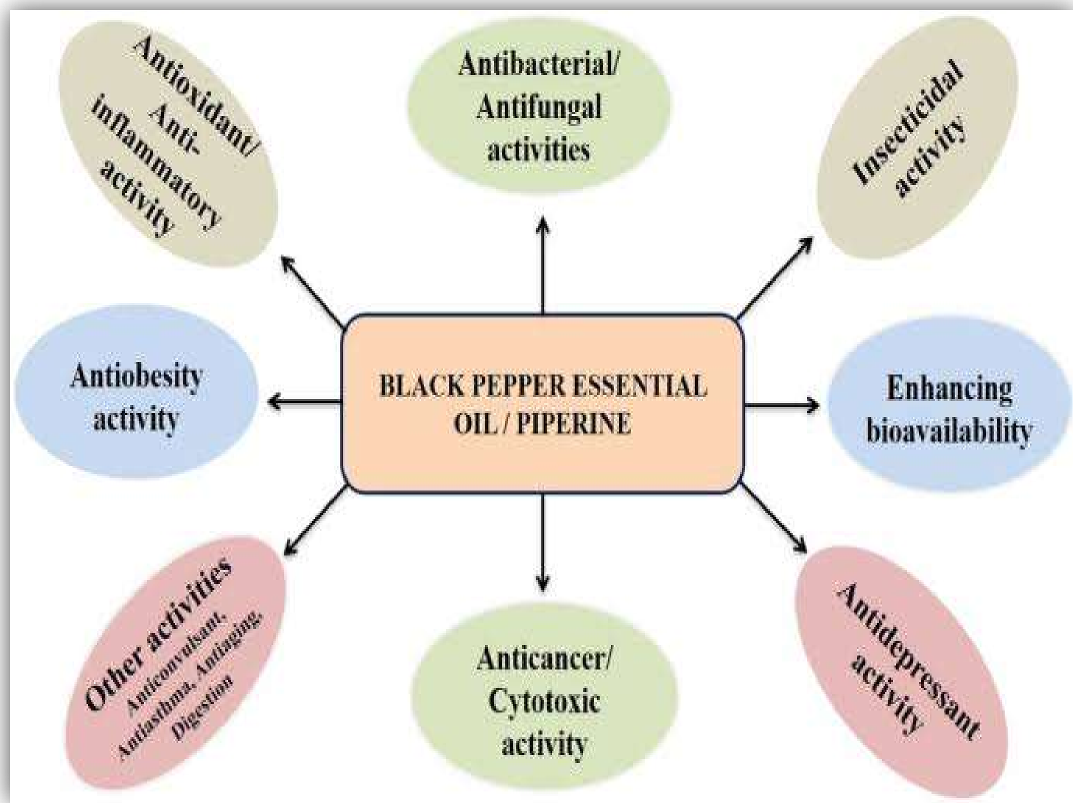

Figure 8: Pharmacological activities of pepper

Various pepper species have different flavours because of an alkaloid known as piperine. It has been discovered in a variety of other plant species in addition to being present in members of the Piperaceae family (Rhododendron faurie, Vicoa indica, Anethum sowa, and others). The plant Piper nigrum L has the highest concentration of piperine, which can range from 2 percent to as much as 9 percent, depending on the growth environment, including the climate and/or place of origin. Black pepper (Piper nigrum L.), the most widely used pepper type, is also a significant medicinal plant in addition to being used as a spice all over the world. Due to its unique role in Ayurvedic medicine, where it acts as one of the "tricatu" components, its traditional use extends back countless years (equal proportions of black pepper, long pepper and ginger). Tricatu or one of its constituent constituents serves as the foundation for 210 of the 370 formulations listed in the Handbook of Common Ayurvedic and Homeopathic Medicines. Traditional uses for pepper include the treatment of fevers, a multitude of gastrointestinal disorders, and broncho-pulmonary and neurological diseases (asthma and chronic bronchitis). Traditional medicine, especially Chinese medicine, use black pepper to treat a number of conditions, including rheumatism, infections like strep throat and influenza, as well as to enhance blood flow (including headaches and muscle discomfort). In addition to lignans, alkaloids, flavonoids, phenols, and amides, pepper also contains fibre, starch, protein, carbohydrates, and essential oil. Chemicals that give the dish its particular flavour and aroma are present in black pepper essential oil, which may be found in the fruits in amounts of up to 3.5 percent. The primary chemical components of this essential oil include sabinene, -pinene and -pinene, -caryophyllene, phellandrene, limonene, linalool, citral, and other substances. Beta-carotene, lauric, myristic, and palmitic acids, as well as piperine, are some of the several compounds found in pepper. One of pepper's primary alkaloids, piperine (piperoylpiperidine), is what gives the spice its flavour and many of its pharmacological effects. A wide spectrum of effects, including antihypertensive, antiaggregant, antioxidant, anticancer, antispasmodic, antiasthmatic, depressed, anxiolytic, and many more physiological qualities, have been identified through studies on the physiological effects of piperine. Along with its numerous biological activities, piperine is well known for its ability to increase a drug's bioavailability, increasing its therapeutic potential. In addition to its beneficial qualities, piperine, the main ingredient of the most popular spice, pepper, has been taken for thousands of years as food with no known negative effects on health. Other studies showed that piperine ingestion was safe due to the absence of piperine genotoxicity in Ames tests and micronucleus testing. The results of human clinical studies are included in this review, together with information from the literature on the numerous biological effects of piperine.

A. Antioxidant effects

Oxidative stress plays a significant role in the development of a number of degenerative and chronic diseases, including cancer, immune system issues, diabetes, and Parkinson's disease. Antioxidants, which can be either natural or synthetic, are used to decrease chronic and degenerative diseases and prevent the generation of free radicals by scavenging them. Benefits of the polyphenolic chemical Hydroxytyrosol (HT), which also has potent antioxidant capabilities, including hydrogen donation and improved radical stability. White adipose tissue (WAT) dysfunction brought on by a high-fat diet (HDF) given to mice is reduced by supplementing with HT through altering the transcription factors NF-B, Nrf2, SREBP-1c, and PPAR- and their target genes, which are involved in inflammation, antioxidant defences, and lipogenesis. Vijayakumar et al. reported that piperine may have potential protective action against lipid peroxidation and antioxidant activity in rats given a high-fat diet that generated oxidative stress to cells. Piperine was most effective against all tested gram positive and negative strains with a minimum inhibitory concentration (MIC) of 325 mg/ml or less and has the strongest antioxidant potential. According to Jeena et al., in vitro tissue lipid peroxidation was decreased and superoxide was scavenged by black pepper essential oil.

B. Antibacterial and antimicrobial effects

Customers frequently favour organic and non-toxic products to protect food from microorganisms while it is being preserved. Food pathogenic bacteria, which can seriously harm people's health, may reappear as a result of prolonged usage of chemical preservatives. Unknown are the bactericidal properties of black pepper. Piperine may have both antibacterial and antifungal effects on *Fusarium oxysporum, Aspergillus niger, Bacillus subtilis, Escherichia coli, Aspergillus niger, (A) flavus,* and *Staphylococcus aureus*. The phenolic compounds present in fresh black pepper seed extracts have the capacity to inhibit *Bacillus, Escherichia coli, Staphylococcus aureus, S. faecalis, and B. cereus.* Black pepper essential oil has the potential to be employed as a natural antibacterial agent in the meat industry, according to Zhang et al. They proved that the lowest inhibitory concentration for meat-borne *E. coli* was 1.0 l/ml of BPEO. Similar to this, BPEO demonstrated potent effectiveness against *E. coli, B. substilis, and S. aureus.*

C. Anticancer effects

On various cancer types, the BPEO and piperine show anti-cancer properties. Both androgen-dependent and androgen-independent prostate cancer cells significantly suppressed tumour growth. Makhov et al. noticed elevated anticancer activity when piperine and docetaxel were given combined to treat human prostate cancer. Piperine caused DNA damage and death in tumour cells, making it a promising therapeutic agent for the treatment of osteosarcoma. By encouraging antioxidant defence enzymes and reducing lipid peroxidation, piperine also reduced lung cancer. The aforementioned comments suggest that piperine may have anticancer effects. However, there have only been a few number of studies that have looked into the anticancer potential of piperine and BPEO, and they have all only employed animal models. Therefore, future studies should concentrate on the bioactivity of BPEO in various human clinical testing.

Breast Cancer: Activating caspase-3 and cleaving PARP resulted in an inhibition of proliferation and an induction of apoptosis, according to a study on breast cancer cells overexpressing HER2. Additionally, it was discovered that piperine inhibits the transcriptional activity of the HER2 gene, increasing the sensitivity of HER2 overexpressing cells to paclitaxel death. The same study found that it suppresses the ERK1/2, p38 MAPK, and Akt signalling pathways, reduces the expression of MMP-9 that is induced by epidermal growth factor, and inhibits the activation of NF-B and AP-1 (EGF). Without impacting the growth of healthy mammary epithelial cells, piperine inhibits the development of triple-negative breast cancer cells (TNBC) and hormone-dependent breast cancer cells in culture. Additionally, it increases the expression of p21(Waf1/Cip1), slows the development of mammospheres, blocks the Wnt signalling pathway, and inhibits the breast stem cell marker ALDH. It also suppresses the survival-promoting Akt activation and the activation of Akt. These all take place without endangering differentiated cells. Adding piperine as an adjuvant to factor-related apoptosis-inducing ligand (TRAIL)-based therapy improved its efficacy, according to a second study on TNBC cells. A time- and dose-dependent reduction in the synthesis of MMP-9 and MMP-13 was observed after piperine (35-280 mol/L) injection into tumours in a model of 4T1 murine breast cancer cells. It has been discovered that the activity of piperine analogues, which are made by substituting other amino acids and aniline in the piperidine nucleus, against human breast cancer cells is considerably boosted. A histidine analogue of piperine with an imidazole ring structure was shown to have the strongest cytotoxic effect (IC50: 0.74 mol).

Lung Cancer: Studies on the effects of piperine on lung cancer came up with some really positive results. By activating the caspase-3 and caspase-9 cascades, stopping the G2/M phase of the cell cycle, and exhibiting particular cytotoxicity against the lung cancer cell line, piperine promotes apoptosis in cancer cells, claim Lin et al (A549). It also improved the Bax/Bcl-2 ratio by upregulating Bax protein expression while downregulating Bcl-2 protein expression. Benzo(a)pyrene induces lung cancer by decreasing glutathione transferase (GST), quinone reductase (QR), and UDP-GT and increasing hydrogen peroxide levels. In the investigation on Swiss albino mice, piperine (50 mg/kg body weight) and benzo(a)pyrene (BaP) were administered orally to animals for 16 weeks. When compared to the control groups, piperine has been demonstrated to have a protective effect against BaP-induced lung carcinogenesis in mice by lowering levels of lipid peroxidation, protein carbonyls, nucleic acid content, and polyamine formation. Piperine produces BaP-induced cytotoxicity in V-79 lung fibroblast cells through lowering GST and UDP-GT. In rats with lung cancer, piperine treatment reduces DNA damage and DNA-protein cross-links. The mitochondrial enzymes isocitrate dehydrogenase (ICDH), ketoglutarate dehydrogenase (KDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH), and glucose-6-phospho dehydrogenase (G6PDH) as well as the glutathione-metabolizing enzymes GPx, GR, and glucose-6-phospho dehydrogenase (G6PDH) Additionally, it was discovered that the sodium/potassium/magnesium ATPase enzyme activities were downregulated in these animals while the ATPase enzymes in erythrocyte membrane and tissues were elevated, highlighting the chemopreventive effect of piperine. In C57BL/6 mice (4270 of 29), lung metastasis caused by B16F-10 melanoma cells was dramatically reduced by piperine co-administration and tumour development. The results showed extremely promising antimetastatic action of piperine as shown by decreased lung collagen hydroxyproline, uronic acid, and hexosamine content, a notable decrease in tumour nodule development and lung size, and decreased serum sialic acid and serum -glutamyl transpeptidase activity.

Prostate Cancer: When it comes to voltage-gated K+ channels (KV), which are regarded to be promising targets for the treatment of cancer and play a crucial role in controlling cancer cell proliferation, it was observed that piperine blocks voltage-gated K+ current. The IC50 was 49.45 M in PC-3 human prostate cancer cells while it was 39.91 M in LNCaP. The G0/G1 cell cycle was arrested as a result of the observed barrier, which therefore impeded cell growth and led to apoptosis. Another study using the human prostate cancer cell lines DU145, PC-3, and LNCaP showed that piperine also caused cell cycle arrest at the G0/G1 stage, downregulated cyclin D1 and cyclin A, and increased levels of p21Cip1 and p27Kip1 following piperine therapy (LNCaP and DU145). Additionally, the increased LC3B-II level and LC3B puncta generation demonstrated that piperine administration improved autophagy. In LNCaP, PC-3, and DU-145 prostate cancer cells, piperine activated caspase-3, cleaved PARP-1 proteins, and reduced the production of phosphorylated STAT-3 and NF-kB transcription factors. A recent study found that the molecular mechanism causing the observed lower cell proliferation and migration (in the PCa DU145 cell line) of piperine activity was the Akt/mTOR/MMP-9 signalling pathway.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: Piperine markedly increased the levels of lipid peroxidation when 7,12-dimethylbenz[a]anthracene (DMBA) produced hamster buccal pouch cancer. The efficiency of piperine as a chemopreventive agent was evaluated by FT-IR spectroscopic analysis, and it was found that treated cancer cells contained fewer proteins and nucleic acids than did untreated cancer cells. In AGS human gastric cancer cells, piperine decreases Bcl-2, XIAP (anti-apoptotic), and Akt while raising p53, Bax (pro-apoptotic), cleaved caspase-9, and cleaved-PARP. Through suppressing IL-1-induced p38 MAPK and STAT3 activation, piperine lowers IL-1-induced IL-6 production in TMK-1 gastric cancer cells. By increasing the levels of the protein Fas and decreasing the levels of the proteins Bcl-2, Mcl-1, and survivin, it also slows the growth of HT-29, human colon cancer cells. Piperine decreases 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 while upregulating the expression of p21/WAF1 and p27/KIP1. According to the research done by Yaffe et al., this natural chemical caused apoptosis in the HRT-18 human rectal cancer cells, which stopped them from growing. This impact was at least partially explained by the fact that the piperine-treated cancer cells produced more reactive oxygen species (ROS), according to the same study. The activation of the mTORC1 mechanistic target of rapamycin complex 1 has been connected to the development of colorectal cancer and persistent inflammation. When combined with curcumin, piperine delays the onset of colorectal cancer by inhibiting TNF- and mTORC1 in human intestinal epithelial cells.

Other Cancer Types: In human fibrosarcoma HT-1080 cells, piperine reduces NF-B and AP-1 activation, inhibits PKC and ERK phosphorylation, and suppresses MMP-9 production. Piperine (2.5, 5 and 10 g/mL) decreased the activity of the transcription factors NF-B, c-Fos, cAMP response element-binding protein (CREB), and activated transcription factor (ATF-2) in B16F10 melanoma cells, which in turn reduced the expression of the inflammatory and growth-regulating genes IL-1, IL-6, TNF-, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Piperine causes the mortality of mouse melanoma cells (B16F10) by boosting intracellular ROS generation, upsetting calcium homeostasis, and lowering mitochondrial membrane potential in cells that have been exposed to ultraviolet B. The human cancer cell lines IMR-32, MCF-7, PC-3, DU-145, Colo-205, and Hep-2 are all fatally affected by synthetic piperine-amino acid ester conjugates.

D. Cytotoxicity effects

BPEO and piperine may assist breast cancer cells more effectively undergo TNF-related apoptosis. Greenshields et al. discovered that piperine and radiation combination exhibited higher cytotoxicity and were more successful at preventing the spread of tripe-negative cancer cells in immune-deficient mice than radiation alone. Despite the safety of piperine and BPEO having been shown, the use of cell lines exclusively in in vitro investigations limits the therapeutic usefulness of this result.

E. Insecticidal effects

European chafer is resistant to the insecticidal effects of black pepper (Amphimallon majale, Coleoptera:Scarabaeidae) According to Upadhyay and Jaiswal, adults of Tribolium castaneum, the primary insect that attacks wheat grain storage, may be repelled by black pepper essential oil at a concentration of 0.2% (v:v) (Herbst). According to Naseem and Khan, using more black pepper essential oil had the most repellant properties when exposed to T. castaneum for the longest periods of time. Since BPEO's insecticidal qualities have only been the subject of two studies so far, more research is needed in this promising field.

F. Anti-inflammatory effect

A medication known as an anti-inflammatory reduces inflammation in the body of an individual. Another one of these ingredients is black pepper. A complex biological response of vascular tissues to harmful stimuli, such as infections, harmed cells, or irritants, is inflammation. As opposed to opioids, which work on the central nervous system, almost half of analgesics are anti-inflammatory drugs, which reduce pain by reducing inflammation. In the long-term management of immune system dysfunction for the treatment of chronic inflammatory diseases like rheumatoid arthritis, anti-inflammatory drugs are routinely employed. Piperine was reported to significantly lower the levels of IL6 and PGE2 in human FLS that had been activated by IL1. PGE2 is essential for triggering pain, hence its synthesis must be suppressed. Both RA and osteoarthritis are affected by MMP1 and MMP13 collagenases, which are the rate-limiting components of the collagen breakdown process. It is essential that MMP13 expression be significantly reduced since it is extremely active against collagen type II, the main collagen in cartilage, and degrades a variety of collagenous and non-collagenous extracellular matrix macromolecules. In IL1-stimulated FLSs, piperine reduces MMP13 expression. An experiment using piperine and carrageenin showed that the increase of the oedema volume was significantly reduced. Piperine significantly influenced early acute modifications in the inflammatory process.

G. Antireproductive Activity

Piperine inhibits Lymnaea acuminata snail reproduction, according to Srivastava et al. They discovered that piperine dramatically reduced this species' fecundity, hatchability, and survival from November 2011 to October 2012. The snails' time to moult is likewise postponed by the piperine treatment. Sublethal piperine treatment caused a significant (p0.05) drop in protein, amino acids, DNA, RNA, and AChE in the ovotestis/nervous tissue of treated snails compared to controls after a 96-hour exposure period. Acetylcholinesterase (AChE) activity in nerve tissue also decreased at the same time. The active component piperine is ineffective against L. acuminata (Piper nigrum). In vitro, the leukotriene and prostaglandin biosynthesis-related enzymes are inhibited by piperine components; the 5-lipoxygenase and COX-1 The cerebral neurosecretory caudo dorsal cells (CDCS) of the fresh water pulmonate snail Lymnaea stagnalis govern egg-laying, a process that involves a pattern of stereotyped behaviour. The CDCS produces and secretes a variety of peptides, including the ovulation hormone (CDCS). Each peptide is thought to govern a certain element of the egg-laying processes. A chemical can either affect RNA synthesis at the transcription stage or the absorption of amino acids in the polypeptide chain to affect protein synthesis in any tissue. These two possibilities could account for the lower protein concentration in the injured tissue. In the first scenario, there would be less RNA and protein content since RNA production would be reduced. In the second case, only the protein content would vary. Piperine inhibits both P-glycoprotein and the essential drug metabolising enzyme CYP3A4. L. acuminata's ovotestis appears to be impacted by the cumulative effects of the molluscicide piperine either directly or indirectly by DCs, which release ovulation hormone and ultimately have an effect on snail reproduction year-round. The AChE activity is one of the biomarkers used in ecotoxicology the most frequently. An essential part of normal cellular neurotransmitter function is continuous nerve firing, which is prevented by the enzyme's breakdown of ACh in cholinergic synapses. Acetylcholinesterase accumulates at the nerve synapses as a result of the AChE inhibition, putting the post synaptic membrane in a continuous state of stimulation that results in paralysis, ataxia, a general lack of coordination in the neuromuscular system, and finally death.

H. Analgesic and anticonvulsant

Due to the desire in discovering new, risk-free natural medicines, researchers are studying P. nigrum as a potential therapeutic painkiller. To assess the analgesic effectiveness of hexane and ethanolic extracts of Piper nigrum and its component piperine, we employed the tail immersion, analgesy-meter, hot-plate, and acetic acid-induced writhing tests. While ethanolextract was most effective after 120 minutes at a dose of 5 mg/kg, piperine's analgesic efficacy peaked in the analgesy-meter test after a dose of 10 mg/kg after 60 minutes (reaction time by mice to remove the tail was 11.658 s).The licking or jumping paw reaction time for piperine in the hot plate method was the quickest (12.870 s after 30 min at a dosage of 10 mg/kg). In the writhing test, acetic acid-induced mouse writhes were completely stopped by piperine (10 mg/kg) and the ethanol extract (15 mg/kg). Investigated was the effect of P. nigrum as an anticonvulsant. Belemkar, Kumar, and Pata (2013) employed the maximal electroshock seizure (MES) induced paradigm and the pentylenetetrazol (PTZ) induced model to find that the ethyl alcohol and hexane extract of P. nigrum decreased the onset and duration of seizures in Wistar rats. Furthermore, Bukhari et al. (2013) found that treating mice with piperine at a dose of 50 mg/kg was more effective than treating them at a dose of 70 mg/kg in preventing PTZ-induced seizures. At the highest studied dose of piperine (70 mg/kg), the latency of convulsions brought on by picrotoxin rose to 878.5 s as opposed to 358.4 s in the control group. both low lipids and low blood sugar Blood glucose levels in diabetic rats who received P. nigrum aqueous seed extract for 4 weeks decreased from 270 mg/100 mL to 129 mg/100 mL. (Kaleem, Sheema, Sarmad, and Bano 2005). Alloxan reduced blood glucose levels in diabetic rats by 100, 200, and 300 mg/kg body weight of P. nigrum leaf methanolic extract after 21 days of therapy (Onyesife, Ogugua, and Anaduaka 2014). Because of the increased polyol pathway activity that leads to the development of long-term diabetic complications, pharmacological inhibition of aldose reductase has been identified as a key strategy in the prevention and attenuation of related complications, particularly retinopathy, neuropathy, and nephropathy. In fact, according to research by Gupta, Singh, and Jaggi in 2014b, the hydromethanolic extract of the seed inhibited goat lens aldose reductase with an IC50 value of 35.64 lg/mL. Rats on the high fat diet showed increased levels of the enzymes lipoprotein lipase (LPL), lecithin-cholesterol acyltransferase (LCAT), and lipoprotein lipase (LPL) compared to rats who did not receive piperine. They also had lower plasma total cholesterol, LDL, VLDL, and HMG CoA reductase levels.

I. Piperine as a recovery molecule for the COVID-19 pandemic

Patients with COVID-19 benefit from stronger immune systems thanks to healthy gut flora. To discriminate between the many microbial metabolites created after piperine and other chemicals acquired from plants have been broken down, LC-MS/MS must be used. Microbial metabolites have the ability to cross the BBB and have pleiotropic effects on the brain and other organs via altering gene expression. By detecting healthy gut microbiomes in stool samples from COVID-19 patients, faecal microbiota transplantation (FMT) technologies may be a more effective way to practise precision medicine.Consuming black pepper may directly aid in the battle against SARS-CoV-2 in addition to its immune-modulating benefits due to potential antiviral properties. A recent study found that piperine can bind to both the cellular receptor for ACE2 and the spike gly-coprotein of the SARS-CoV-2 virus. It was found that interactions of hydrogen bonds with Gly399, His401, Glu402, Arg514, and Arg518 were significant by producing one predictable hydrogen bond with each amino acid residue. When piperine interacts with the main pro-tease, a hydrogen bond is created with His41, with a docking score of -90.95 and a binding energy score of -78.10kcal mol1. Alkyl interactions, -sul-fur, -, and T-shaped contacts are further stabilising interactions. Van der Waals interactions with the SARS-CoV-2 receptor-binding domain spike protein's ARG71, TYR121 (TYR453), TYR163 (TYR495), and ASN169 (ASN501) further regulate piperine's binding process. The binding affinity of piperine is 6.4 kcalmol-1 (RBD Spro). Piperine and SARS-CoV-2 RBD Spro stabilised each other primarily through covalent hydrogen bonds, T-shaped interactions, and van der Waals forces. Piperine interferes with the viral protein Nsp15 to stop SARS-CoV-2 replication. Additionally, the interactions between piperine and curcumin enhance curcumin's bioavailability, enabling it to bind to the RBD Spro and ACE-2 receptors in the host cell and obstruct virus entry.

J. Enzyme-Related Activity

Monoamine Oxidase Activity Piperine mimics the actions of antidepressants by regulating the monoaminergic system. A biochemical marker of the monoaminergic system is the monoamine oxidase (MAO) concentration, and piperine has been found to inhibit this enzyme. The IC50 values for piperine's inhibition of monoamine oxidase-A and -B were 20.90 and 7.00 M, respectively. The effects of piperine and its derivatives antiepilepsirine, methylpiperate, guineensine, and piperlonguminine were comparable. When coupled with ferulic acid, piperine exhibits a synergistic effect on MAO inhibition.. 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. Piperine increased the ratios of phospho-AKT1 (pAKT1)/AKT1, phospho-AKT2 (pAKT2)/AKT2, and phospho-ERK1/2 (pERK1/2)/ERK1/2 in the testis of rats. In stressed mice, piperine raises GABA levels and decreases neuronal NOS, resulting in anti-anxiety action. According to studies on piperine's effect on microsomal P450s, when piperine was provided to mice, P4501A and P4502B expression increased while P4502E1 expression decreased. Acute acetaminophen overdose results in increased AST and ALT levels in hepatotoxic rats. Increased levels of these enzymes are prevented by pretreatment with piperine. In a study using a rat intestinal lumen model to examine piperine's free radical scavenging abilities, piperine considerably raised GSH levels (exposed to hydrogen peroxide and cumene hydroperoxide). Piperine inhibits DNA binding-1, runt-related transcription factor 2, and AMPK phosphorylation to increase osteoblast development in MC3T3-E1 cells (Runx2). In mice with ovalbumin-induced asthma, piperine reduces cyclooxygenase-2 expression in macrophages, NF-B, C/EBP, and c-Jun nuclear translocation, Akt, and ERK activation, as well as T cell activity and Th2 cytokine secretion. In rats with pilocarpine-induced epilepsy, piperine acts as an anticonvulsant by increasing caspase 3 and lowering Bax/Bcl 2.

Piperine reduces the serum levels of thyroxin, triiodothyronine, and glucose in adult male Swiss albino mice, as well as the 50D enzyme and glucose-6-phosphatase in the liver. The enzyme activity is comparable to that of the common antithyroid drug propylthiouracil. Piperine inhibits two carbonic anhydrases (CAs), human cytosolic isoforms hCA I and II. Numerous physiological and pathological processes, including the emergence of cancer, are mediated by these enzymes. Through their catalysis, CO2 is changed into the bicarbonate ion and protons in a physiological reaction. 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. Numerous physiological and pathological processes, including the emergence of cancer, are mediated by these enzymes. Through their catalysis, CO2 is changed into the bicarbonate ion and protons in a physiological reaction. The finding of piperine's inhibitory impact against CAs highlights its potential as an anti-convulsant, analgesic, anti-tumor, and anti-obesity medication.

K. Effect on Immunity and Allergic Response

There is a lot of promise for piperine's immunomodulatory properties. Reduced 5-FU IC50 values are proof that piperine enhanced 5-fluorouracil (5-FU) growth suppression when it was incubated with tumour cell lines, according to Bezerra et al. Piperine was used concurrently with 5-FU to lessen leucopoenia, showing improved immunocompetence that was suppressed by 5-FU. In the work by Bernardo et al., it was found that the proliferative response brought on by lipopolysaccharide (LPS) and immunoglobulin -IgM antibody is inhibited in vitro by piperine. The effects of piperine on B cell activity and the humoral immune response to T-un/dependent antigens were investigated in this study. Piperine also prevented the synthesis of IgM antibodies and decreased the expression of the CD86 cluster of differentiation. According to a recent study by Lee et al., the combination of piperine and gamma-aminobutyric acid (GABA) activated p38 and JNK MAPK, upregulating NF-B and IL-10 while enhancing the production of EPO and EPO-R. In mice with allergic rhinitis caused by ovalbumin, piperine exhibits a notable anti-allergic impact in addition to immunomodulation. Piperine also greatly decreased the histamine released as a result of an antigen-antibody reaction, which results in sneezing, rubbing, and redness. Lower eosinophil migration into nasal epithelial tissue, however, negated this effect. It was found that piperine treatment decreased inflammation, redness, and disruption of the alveoli and bronchioles, similar to the histological section of the nasal mucosa. In an ovalbumin-induced asthma model, piperine therapy lowered eosinophil infiltration and decreased airway hyperresponsiveness via lowering T cell activity and Th2 cytokine production.

L. Effects of Piperine on Other Neurological Processes and Neuroprotection

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 acetic acid and hot plate response tests, 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.

Consequences of Piperine : Piperine is severely toxic 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 former study's findings only demonstrated that piperine had detrimental effects on the testes when it was administered to mature male albino rats for 30 days at levels of 5 and 10 mg/kg. The study found that lower doses resulted in partial degeneration of different germ cell types, whereas higher doses resulted in severe damage to the seminiferous tubule, a reduction in caput and cauda epididymal sperm concentrations, a reduction in seminiferous tubular and Leydig cell nuclear diameter, and desquamation of spermatocytes and spermatids. Additionally, the blood gonadotropin levels in these piperine-treated rats increased whereas the intratesticular T concentration decreased.

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 research is necessary to examine the system of action of plant extracts in the animal body.

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