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

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ABSTRACT

The ayurvedic medicine domain solutions to a host of problems that we experience on a regular basis with potentially zero side effects. Black pepper certainly has an irreplaceable place in ayurvedic medicine, and its regular consumption can help you entail numerous health benefits. Considered as the "King of spices", black pepper (Piper nigrum L.) is a widely used spice which adds flavor of its own to dishes, and also enhances the taste of other ingredients. *Piper nigrum* has also been extensively explored for its biological properties and its bioactive Phyto-compounds. There is, however, no updated compilation of these available data to provide a complete profile of the medicinal aspects of P. nigrum. This study endeavors to systematically review scientific data on the traditional uses, phytochemical composition, and pharmacological properties of *P. nigrum.* Information was obtained using a combination of keywords via recognized electronic databases (e.g., Science Direct and Google Scholar). Google search was also used. Books and online material were also considered, and the literature search was restricted to the English language. The country with the highest number of traditional reports of P. nigrum for both human and veterinary medicine was India, mostly for menstrual and ear-nose-throat disorders in human and gastrointestinal disorders in livestock. The seeds and fruits were mostly used, and the preferred mode of preparation was in powdered form, pills or tablets, and paste. Piper nigrum and its bioactive compounds were also found to possess important pharmacological properties. Antimicrobial activity was recorded against a wide range of pathogens via inhibition of biofilm, bacterial efflux pumps, bacterial swarming, and swimming motilities. Studies also reported its antioxidant effects against a series of reactive oxygen and nitrogen species including the scavenging of superoxide anion, hydrogen peroxide, nitric oxide, DPPH, ABTS, and reducing effect against ferric and molybdenum (VI). 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

Black pepper is a flowering vine, cultivated for its fruit, which is usually dried and used as a spice and seasoning. Black pepper is native to South India and is extensively cultivated there and elsewhere in tropical regions. The pepper plant is a perennial woody vine growing to 4 m in height on supporting trees, poles, or trellises. It is a spreading vine, rooting readily where trailing stems touch the ground. The leaves are alternate, entire, 5-10 cm long and 3-6 cm broad. The flowers are small, produced on pendulous spikes 4-8 cm long at the leaf nodes, the spikes lengthening to 7-15 cm as the fruit matures. 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 aroma through evaporation, so airtight storage helps preserve its spiciness longer. Pepper can also lose flavour when exposed to light, which can transform piperine into nearly tasteless isochavicine. Once ground, pepper's aromatics can evaporate quickly; most culinary sources recommend grinding whole peppercorns immediately before use for this reason. Handheld pepper mills or grinders, which mechanically grind or crush whole peppercorns, are used for this as an alternative to pepper shakers that dispense ground pepper. Dried ground pepper has been used since antiquity for both its flavour and as a traditional medicine. Black pepper is the world's most traded spice. It is one of the most common spices added to cuisines around the world. The spiciness of black pepper is due to the chemical piperine, not to be confused with the capsaicin characteristic of fresh hot peppers. Black pepper is ubiquitous in the modern world as a seasoning and is often paired with salt.Spice mills such as pepper mills were found in European kitchens as early as the 14th century, but the mortar and pestle used earlier for crushing pepper have remained a popular method for centuries, as well.Enhancing the flavour profile of peppercorns (including piperine and essential oils), prior to processing, has been attempted through the postharvest application of ultraviolet-C light (UV-C).

Piper nigrum (Black pepper) is one of the most commonly used spices and considered as "The King of Spices" due to its trade in the international market. It is commonly known as Kali Mirch in Urdu and Hindi, Pippali in Sanskrit, Milagu in Tamil and Peppercorn, White pepper, Green pepper, Black pepper, Madagascar pepper in English.Black pepper is used as medicinal agent, a preservative, and in perfumery. The genus Piper has more than 1000 species but the most well-known species are Piper nigrum, Piper longum and Piper betli. Black pepper can be used for many different purposes such as human dietaries, as medicine, as preservative, as biocontrol agents. Pepper is used worldwide in different types of sauces and dishes like meat dishes. It contains major pungent alkaloid piperine (1-peperoyl piperidine) which is known to possess many interesting pharmacological actions. Tiwari and Singh reported that this plant and its active components piperine can stimulate the digestive enzymes of pancreas and intestine and also increases billiary bile acid secretion when orally administered. Blackpepper is important for its medicinal values medicinally black pepper can be used digestive disorder like large intestine toxins, different gastric problems, diarrohea and indigestion and also can be used against respiratory disorder including cold fever, asthama. Piperine exhibits diverse pharmacological activities like antihypertensive and anti-platelets, antioxidant, antitumor, antipyretic, analgesic, anti-inflammatory, antidiarrheal, antispasmodic, hepato-protective, antibacterial, antifungal, anti-thyroids, anti-apoptotic, anti-spermatogenic, insecticidal and larvicidal activities etc. Piperine has been found to enhance the therapeutic efficacy of many drugs, vaccines andnutrients by increasing oral bioavailability by inhibiting various metabolising enzymes processed peppercorns come in a variety of colours, any one of which may be used in food preparation, especially common peppercorn sauce. Black pepper is produced from the still-green, unripe drupe of the pepper plant. The drupes are cooked briefly in hot water, both to clean them and to prepare them for drying. The heat ruptures cell walls in the pepper, speeding the work of browning enzymes during drying. The drupes dry in the sun or by machine for several days, during which the pepper skin around the seed shrinks and darkens into a thin, wrinkled black layer. Once dry, the spice is called black peppercorn. On some estates, the berries are separated from the stem by hand and then sun-dried without boiling. After the peppercorns are dried, pepper spirit and oil can be extracted from the berries by crushing them. Pepper spirit is used in many medicinal and beauty products. Pepper oil is also used as an ayurvedic massage oil and in certain beauty and herbal treatments. White pepper consists solely of the seed of the ripe fruit of the pepper plant, with the thin darker-coloured skin (flesh) of the fruit removed. This is usually accomplished by a process known as retting, where fully ripe red pepper berries are soaked in water for about a week so the flesh of the peppercorn softens and decomposes; rubbing then removes what remains of the fruit, and the naked seed is dried. Sometimes the outer layer is removed from the seed through other mechanical, chemical, or biological methods. Ground white pepper is commonly used in Chinese, Thai, and Portuguese cuisines. It finds occasional use in other cuisines in salads, light-coloured sauces, and mashed potatoes as a substitute for black pepper, because black pepper would visibly stand out. However, white pepper lacks certain compounds present in the outer layer of the drupe, resulting in a different overall flavour. Green pepper, like black pepper, is made from unripe drupes. Dried green peppercorns are treated in a way that retains the green colour, such as with sulfur dioxide, canning, or freeze-drying. Pickled peppercorns, also green, are unripe drupes preserved in brine or vinegar. Fresh, unpreserved green pepper drupes are used in some cuisines like Thai cuisine and Tamil cuisine. Their flavour has been described as "spicy and fresh", with a "bright aroma."They decay quickly if not dried or preserved, making them unsuitable for international shipping. Red peppercorns usually consist of ripe peppercorn drupes preserved in brine and vinegar. Ripe red peppercorns can also be dried using the same colour-preserving techniques used to produce green pepper. Pink peppercorns are the fruits of the Peruvian pepper tree, Schinus molle, or its relative, the Brazilian pepper tree, Schinus terebinthifolius, plants from a different family (Anacardiaceae). As they are members of the cashew family, they may cause allergic reactions, including anaphylaxis, for persons with a treenut allergy.

II. INDIAN BLACK PEPPER VARIETIES

Each producing country has identified and developed for cultivation a number of pepper varieties most suitable for the conditions prevailing in their pepper growing regions. These varieties vary in growth characteristics and yield. Since these varieties are suited to the agro-climatic conditions existing in each region, it is not desirable to use varieties from other regions as planting material without confirming their suitability in appropriate trials and scientific studies. In India over 75 varieties or cultivars of pepper are grown. Karimunda is the most popular among them. Other important varieties are Kottanadan, Narayakodi, Aimpiriyan, Neelamundi, Kuthiravally, Balancotta, and Kalluvally in Kerala State and Billimalligesara, Karimalligesara, Doddigya, Mottakare and Uddagare in Karnataka State. Some of these cultivars have been used for selection of high yielding varieties and for hybridization programmes. The first hybrid, Panniyur 1 (Fig below), was produced at Panniyur Pepper Research Station in Kerala over three decades ago. This hybrid variety is very popular among pepper farmers in India. Kottanadan is good for extraction of oleoresin. At present 12 varieties have been released including Panniyur 1 for cultivation in India by different research stations located at Kozhikode, Panniyur and Palode, in Kerala.

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 all possess certain common traits. Cells of these organisms possess a true nucleus and membrane bound organelles.
Plant: Kingdom belonging to the eukaryotic supergroup Archaeplastida. Organisms in this kingdom are multicellular, contain celluose as a structural element of their cell walls, and contain chloroplasts which allow the organisms to conduct photosynthetic activity.
Magnoliophyta ("Angiospermae" or "flowering plants"): This division of Kingdom Plantae contains organisms who produce covered seeds, flowers, endosperm, and stamens.
Magnoliopsida ("Dicotyledons, Dicots"): Members of this class produce an embryo with paired cotyledons and possess a net-like veination structure in their leaves. Piper plants are neither monocot or eudicot (true dicotyledon).
Piperales: Order of dicot flowering plants containing herbs, shrubs, and small trees. Members of this order have small flowers clustered together in cone shaped structures.
Piperaceae("Pepper" family): Family of Piperales who generally live in warm, tropical, foliated and shady habitats.
Piper: Genus of plants that contains pepper vines. This term comes from the ancient Tamil word pippali meaning long pepper. The word "pepper" has been applied to similarly spicy plants over history, resulting in the naming of common chile "peppers" and similar members of the genus Capsicum which contain the spicy hot chemical capsaicin.
Piper nigrum: Specific species known commonly as black pepper which derives its name from the Latin words for ""pepper" and "black."

IV. BOTANICAL DESCRIPTION

It is a small, perennial climber, an aromatic shrub that belongs to the Piperaceae family. The roots of the plant are woody, wide ovate with cordate leaves. The stem is creeping, jointed and thickened at the nodes. The leaves are spreading, alternate, without stipules and with blades that varies greatly in size. The lowest leaves are 5-7 cm long and the uppermost leaves are 2-3 cm long.Flowers are cylindrical with solitary spikes. The fruits are small, ovoid that grow in fleshy spikes, blunt, oblong, blackish-green with length 2.5-3.5 cm and 5 mm width. The mature spikes are long, cylindrical, and oblong. The berries are red or black with aromatic odor and pungent taste that is collected and dried as the commercial form of pippali. The root radix is known as pippalimula. Plants are often rhizomatous, and can be terrestrial or epiphytic. The stems can be either simple or branched. Leaves are simple with entire margins, and are positioned at the base of the plant or along the stem, and can be alternate, opposite, or whorled in arrangement. Stipules are usually present, as are petioles. The leaves are often noticeably aromatic when crushed.Flowers Inflorescences (in the form of spikes) are terminal, opposite the leaves, or located in the axils. Flowers are bisexual, with no perianth, each flower is subtended by a peltate bract. Stamens are 2–6, and hypogynous, with 2-locular anthers. There are usually 3-4 stigmas attached to a single pistil per flower, which is 1 or 3-4 carpellate. The ovary is 1 locular, and superior.Fruits are drupelike, with a single seed per fruit. The seeds have a minute embryo, and mealy perisperm.

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. One tablespoon of black pepper contains 4.4 grams of carbohydrates. In cooking, typically less than 1 tablespoon is used. This would have almost no effect on blood sugar levels and the amount of carbohydrates added to the dish is virtually insignificant. There are almost 2 grams of fiber in 1 tablespoon of black pepper, making the glycemic effect and impact on blood sugar minimal. It contains an insignificant amount of fat and is cholesterol-free and very small amount of protein. Be sure to include other sources of protein in your diet. Black pepper is a good source of many vitamins and minerals. It also is an excellent source of manganese, which is important for bone health, wound healing, and a healthy metabolism. Black pepper is also a significant source of vitamin K, necessary for blood clotting, bone metabolism, and regulating blood calcium levels. Additionally, black pepper contains vitamin C, vitamin E, vitamin A, B vitamins, calcium, and potassium. CaloriesAt 17 calories per tablespoon, black pepper is not a significant source of calories. See the table below for in depth analysis of nutrients:

Table 2: Nutritional value per 100 g. (Source: USDA National Nutrient data base)

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

It is a native species of the Indo-Malaya region. It is mainly grown in limestone soil and heavy rainfall areas having high humidity. Currently, this crop is chiefly cultivated in the tropical regions of the world, such as India, Vietnam, Malaysia, Indonesia, China, and Brazil, and, on a smaller scale, in Sri Lanka and in the West Indies.Vietnam is the world leader in the production of black pepper, producing 163,000 tons which are about 34% of the world's production. The plant is a traditional cash crop in the country, and 95% of the black pepper produced is for export primarily to the US, India, the Netherlands, and Germany. Indonesia is the second largest producer at 89,000 tons while India produces 53,000 tons. Top black pepper-producing regions in India are Kerala, Karnataka, Konkan, and Tamil Nadu. Other countries on the list are Brazil (42,000 tons) and China (31,000).

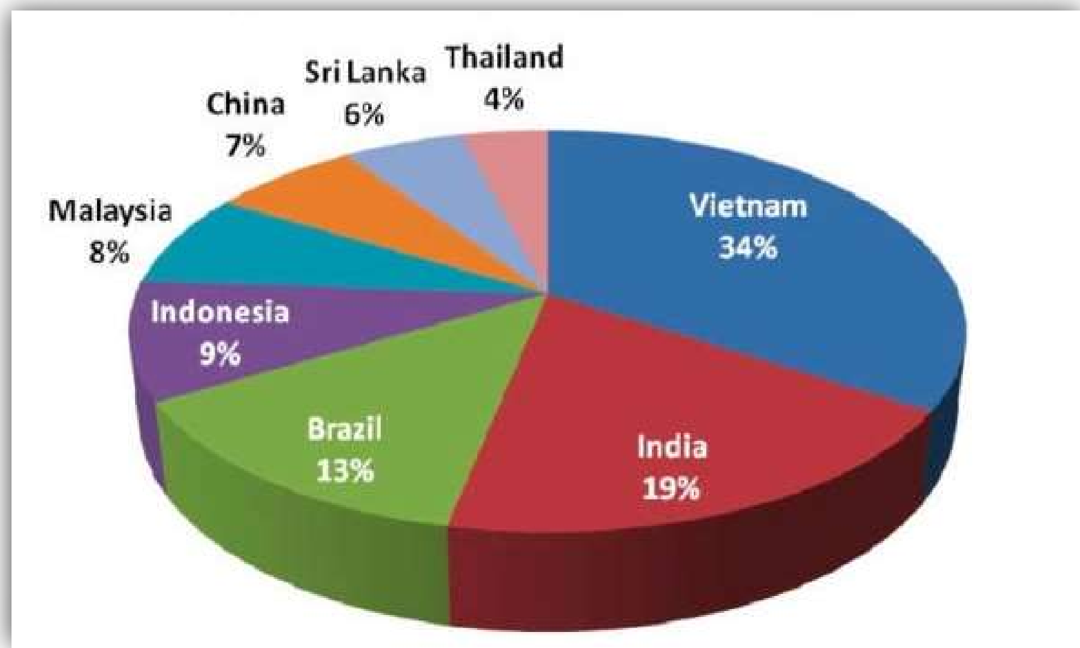

Figure 4: Percentage share of major pepper producing countries

Figure 5: Major Pepper cultivation in India

VII. PHYTOCHEMISTRY OF PEPPER

A. Proximate, minerals, vitamins and bioactive metabolites

Black pepper is rich in minerals, vitamins and nutrients. The chemical composition of 100 g of black pepper seeds includes carbohydrate 66.5 g, protein 10 g, and fat 10.2 g , as well as a relatively high concentration of minerals such as calcium (400 mg), magnesium (235.8- 249.8 mg), potassium (1200 mg), phosphorus (160 mg), and the lower concentration of sodium, iron and zinc . These minerals are essential elements for dayto-day activities of humans. Besides, black pepper also has a significant concentration of vitamins such as Vitamin C, B1, B2 and B3. Nine accessions of Nigeria grown black pepper had a concentration of tannin ranging from 2.11 to 2.80 mg /100 g. In a recent study on black pepper, Ashokkumar et al reported flavonoids such as catechin, quercetin and myricetin, and carotenoids, namely lutein and β-carotene was detected in significant concentration.

B. Essential oil, Oleoresin and Piperine

Several researchers evaluated essential oils (EO), oleoresin and piperine in various parts of black pepper.The EO yield of black pepper berries and leaves have varied from 1.24 to 5.06 %, and 0.15–0.35 %, respectively. However, the oil yield depends on the variety, area and age of the product, parts and methods used.Kurian et al. observed variability of volatile oil and oleoresin content in 14 black pepper accessions ranging from 2.7 − 5.1 % and 7.6 −9.4 %, respectively. These researchers reported that volatile oil content was positively correlated with oleoresin and suggested concurrent improvement of these characters by simple selection programme is the best tool for improvement of quality traits in black pepper. Kurian et al.also reported classical hydro-distillation as a better method of volatile oil estimation compared to other techniques.The oleoresin content of black pepper ranged between 4.27 and 12.73 % and the characteristic natural alkaloid of black pepper "piperine" ranged from 2.13 − 5.80 % and 0.12 − 20.86 %, in seeds and leaves correspondingly. The EO profile of black pepper seeds from south India is predominately comprised of β-caryophyllene followed by limonene, sabinene, α-pinene, β-bisabolene, α-copaene α-cadinol, α-thujene, α-humulene; pepper leaves were rich in nerolidol followed by α-pinene and β-caryophyllene. Likewise seeds from Bangladesh were contained EO consisting of β-caryophyllene (18.39 %) followed by α-pinene (16.68 %), limonene (16.16 %), β-pinene (13.61 %), δ -3-carene (9.23 %), β-phellandrene (3.16 %), copaene (3.13 %), 1- napthalenol (3.0 %), and β-myrcene (2.89 %). EO of seeds from Sri Lanka, Malaysia, and Brazil showed some noticeable variations in major metabolites. The molecular structures of major essential oil constituents isolated from pepper seeds and leaves were drawn by ChemDraw software The yield of minor EO of black pepper contained β-Elemene (1.74 %), δ-Elemene (0.60 %), α-Cubebene (0.99 %), α- Guaiene (0.36 %), α-Zingiberene (0.74 %), p-Cymene (0.70 %), Bicyclogermacrene (0.31 %), γ-Cadinene (0.65 %), γ-trans-Bisabolene (1.39 %), Hedycaryol (0.37 %), and Germacrene D (0.22 %).

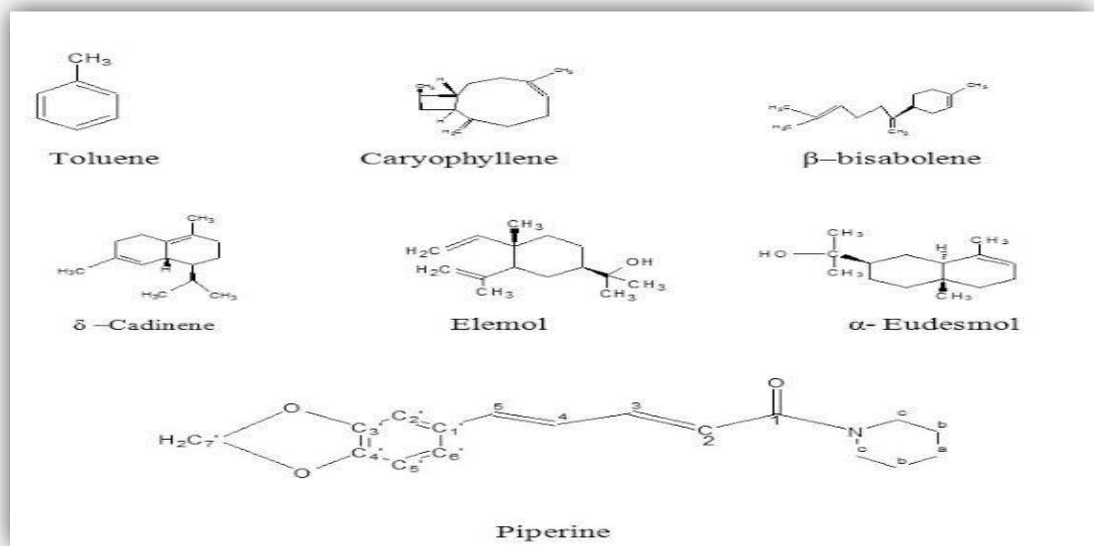

Figure 6: Structure of various components present in pepper plant

VIII. AYURVEDIC HEALTH BENEFITS OF BLACK PEPPER

Pepper was a key component in the ancient ayurvedic system of medicine. There are numerous records of pepper's medical use in India that date back at least 3000 years. Pepper was a key component in the ancient Ayurvedic system of medicine. It also found its way to China in antiquity. There is written evidence that it was being traded overland from India to Sichuan Province by the 2nd century BCE. Pepper is also mentioned in histories of the Han Dynasty (202 BCE - 220 CE) published in the 5th century CE and in a Tang Dynasty account four centuries later. Pepper was probably brought to China from India initially for medicinal purposes, but it did not take long for it to become an important spice in food. Pepper was also important in Egypt by the time of the New Kingdom (c. 1570 - c. 1069 BCE), as it was found stuffed in the nostrils of the mummy of Ramesses II who died in 1213 BCE. Little else is known about how the Egyptians used pepper or the full details of how it got there, but it is known that there was active trade between India and Arabia by that time, and the Egyptians were sending ships down the Nile to what they called the Land of Punt to obtain exotic goods like frankincense, myrrh, and cinnamon.

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 Samita 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. The ayurvedic medicine domain solutions to a host of problems that we experience on a regular basis with potentially less side effects. Black pepper certainly has an irreplaceable place in ayurvedic medicine, and its regular consumption can help you entail numerous health benefits. Throughout India’s long Ayurvedic tradition, pepper has been a widely used, versatile plant, and often prescribed for its healing and balancing effectsAccording to Ayurveda’s classification, pepper is heavy, slightly oily, and has moisturizing properties. The long pepper is a powerful healing plant with a quick and almost immediate effect after consumption. Black pepper is a rich source of antioxidants. These antioxidants work to fight free radicals, which are molecules, generated both outside and inside our body. Also, Free radical generation and damage happen through chemicals, toxins, pollutants, pollution, harmful rays, etc. Some of these free radicals are also created naturally, while exercising, digesting food, etc. Exposure to these free radicals leads to bodily damage and may lead to significant health problems. Black pepper is a wonderful spice that has several health benefits. Aside from its distinctive flavour that makes it a key component of a variety of cuisines, it has some key medicinal properties that make black pepper an inseparable constituent of ancient Ayurveda medicine. Let’s explore a few benefits of black pepper as denoted by ayurvedic medicine science.

A. Black Pepper Treats Coughs and Colds

Cold and cough are one of the most common respiratory problems that affect all of us.Black pepper is a major component of Ayurvedic medicines that have been used for as long as a cure for these problems. These medicines provide relief from nasal congestion and help in the removal of mucus from the respiratory tract, for a faster recovery. Black pepper can be added to green tea, or with lukewarm water along with turmeric. Old Ayurveda remedy for cold and cough – Black pepper, a pinch of turmeric, 2-3 drops of honey – mix well and consume with lukewarm water.This concoction is extremely healthy and the antimicrobial potential and gastro-protective modules present in black pepper are also known to be an immunity booster.

B. Pepper Benefits Your Brain

Black pepper has a stimulatory effect on our brain. It especially helps patients with neurodegenerative diseases. It improves memory and cognitive function in an individual by stimulating the chemical pathways in the brain.Additionally, it also acts as an antidepressant and elevates an individual’s mood. Black pepper contains the compound piperine, which has been shown to improve cognitive ability in animal studies.It also has shown promising results in preventing Parkinson’s disease by triggering the production of dopamine in the brain, the absence of which causes the disease.

C. Black Pepper Helps Control Blood Sugar

Black pepper is useful in controlling the sugar level in patients with type 2 diabetes. Type 2 diabetes is caused when the pancreas in our body is not able to produce enough insulin or when the body stops reacting adequately to otherwise normal levels of insulin.

For this, nutritionists often claim that adding black pepper to your diet can help lower the risk of high blood sugar. Black pepper’s antioxidant properties help to stabilize blood sugar, while also boosting the digestive tract’s health. In addition to this, black pepper helps to fight obesity, which is also one of the major contributing factors of diabetes.

D. Black Pepper Helps Lower Cholesterol Levels

Congestive heart failure is one of the most common diseases and is a leading cause of death worldwide.High blood cholesterol and hypertension are the most common causes of this disease. Studies have suggested that black pepper can lower the levels of blood cholesterol.Piperine in black pepper helps reduce cholesterol uptake, reduces the levels of ‘bad’ cholesterol (LDL- Low-density lipoprotein) while simultaneously increasing the levels of high-density lipoprotein ‘good’ cholesterol (HDL- High-density lipoprotein).It is proved that dietary intake of black pepper has shown a positive effect lipid regulation.

E. High in Cancer-fighting Properties

Black pepper has also been shown to have anti-carcinogenic properties. The compound piperine, with its antioxidant properties, reduces damage to your cells and keeps the tissues healthy. Thus, eating freshly ground black pepper can help you to keep cancer at bay, due to its anti-inflammatory, antibacterial and antioxidant effects.

F. Pepper Helps in the Absorption of Nutrients

Black pepper helps to increase the absorption of essential nutrients. Due to its inhibitory activity on drug metabolising enzymes, it can help to increase the bioavailability of some nutrients like calcium and selenium, as well as beneficial components found in green tea and turmeric.

G. Pepper Stimulates Digestion

Black pepper helps in the process of digestion. It has been found to have a stimulatory effect on the entire digestive system.Piperine, found in black pepper, stimulates the secretion of hydrochloric acid (HCl) in the stomach, which again helps to digest proteins. It also flushes out toxins from the intestine and helps resolve gastrointestinal disorders.However, it should be added to your diet after consulting a doctor if one is pregnant or on medication.

H. Pepper Enables Fat Loss

Black pepper supports weight loss efforts. It helps to break down fat cells, and also plays a significant role in increasing the levels of metabolism in the body.This increased metabolism allows for an increased breakdown of lipids. Its outer layer contains phytonutrients that induce the breakdown of fat cells and help you lose weight.

I. Black Pepper Treats Skin Problems

Black pepper is known to prevent excessive skin pigmentation. Vitiligo is a skin condition which results in the appearance of discoloured patches over different areas of the body. It occurs when the skin loses the pigment cells (melanocytes).These cells produce the pigment melanin, which gives the skin its colour. Black pepper helps prevent vitiligo and maintains the original colour of the skin. Additionally, black pepper may also help to clear acne by doing away with the intoxicants in it.

J. Alleviating arthritis pain

The hot nature of black pepper results in the improvement of blood circulation and also reduces joint inflammation in Arthritis patients. Ayurveda also points out that black pepper can help in flushing the uric acid from your body, a key factor in body pain.

K. Helps in the treatment of depression

The ayurvedic health benefits of black pepper also include the treatment of depression. It has the potential for instantly enhancing cognitive brain function and also slows down the signs of brain ageing along with memory enhancements. These factors collectively lead black pepper to be used as an excellent depression-fighting ayurvedic medicine.

L. Pepper in the treatment of fever and malaria

The advantage of utilizing black pepper (as opposed to the standard quinine) in the treatment of refractory intermittent fevers, which are symptomatic of malarial infections, was reported by Dr. C. S. Taylor in The British Medical Journal, September 1886. At a 1983 symposium in Bombay, India entitled "Therapeutic Approaches to Malaria" sponsored by Ciba Geigy, Ltd., long pepper was discussed as a possible treatment for chronic malaria. It was reported that long pepper was used for patients with chronic malaria with splenomegaly (enlarged spleen). Long pepper fruits were given in an increasing dose from 3 to 30, starting with 3 and increasing daily by 3 fruits. Subsequently the dose was decreased from 30 to 3 fruits, by reducing 3 fruits daily. Long pepper was boiled in milk and water and drank once a day in the early morning. Drinking this decoction reportedly caused cessation of malarial parasite multiplication and regression of splenomegaly. In traditional Chinese medicine, black pepper has been used for the treatment of epilepsy. Based on this traditional application, a new antiepileptic drug called Antiepilepserine has recently been synthesized by Chinese researchers. Antiepilepserine is a chemical relative of piperine, the main alkaloid phytochemical found in plants of the family Piperaceae. In traditional Middle Eastern medicine, black pepper has been used as a nerve tonic. Recently, the analeptic (nervous system stimulant) properties of piperine have been studied. Based on this research, piperine has been used successfully to counteract morphine-induced respiratory depression in experimental animals.

M. The application of pepper in respiratory diseases

Long pepper, and to a lesser extent trikatu, have been used in the treatment of asthma and chronic bronchitis in Ayurveda and Unani medicine. In a study involving 240 children of different age groups suffering from frequent asthma attacks, long-term administration of long pepper fruits significantly reduced the frequency and severity of the attacks. Twenty-five patients in the study group showed no recurrence of asthma attacks, 161 showed clinical improvement, 47 did not benefit from the treatment, and 7 patients deteriorated. In another study, 20 pediatric patients with asthma received long pepper in doses ranging from 9.35 to 15.75 gm daily for several weeks. As a result of this treatment all patients showed clinical improvement.

N. Bioavailability enhancement : a significant application of pepper

The use of black pepper, long pepper, or trikatu is traditionally well-known in the treatment of a variety of gastrointestinal disorders, and all three act to improve digestion. In the 1920's Bose, an acknowledged author of "Pharmacographia Indica", reported an enhanced antiasthmatic effect of an Ayurvedic formula containing vasaka (Adhatoda vasica) when administered with long pepper. In his "Pharmacopoeia lndica", Bose describes examples of his preparation which consists of juice from the vasaka leaves boiled with sugar, long pepper and butter; then this mixture was added to honey and given as a treatment for asthma. Through sustained experimentation and observation, ancient practitioners discovered herbal agents, such as pepper, which could increase the digestibility and efficacy of both nutrients and herbal drugs.bThe main purpose of trikatu's incorporation into numerous Ayurvedic formulations was most probably to enhance the efficacy of pharmacologically active ingredients. Several groups of investigators now attribute this bioavailability enhancing property of pepper to its main alkaloid, piperine. Piperine is an alkaloid with the molecular formula C17Hl9O3N, which on hydrolysis with alkali gives piperic acid and piperidine.l8 The piperine content of pepper is directly proportional to its pungency. The biological properties of piperine have been extensively studied only in recent years. The proposed mechanism for the increased bioavailability of drugs co-administered with piperine is attributed to the interaction of piperine with enzymes that participate in drug metabolism, such as mixed function oxidases found in the liver and intestinal cells. Interaction with the synthesis of drug chelating molecules in the body such as glucuronic acid has also been proposed. Piperine may also interact with the process of oxidative phosphorylation, or the process of activation/deactivation of certain metabolic pathways, slowing down the metabolism and biodegradation of drugs. This action of piperine results in higher plasma levels of drugs, rendering them more available for pharmacological action. One of the first scientific experiments to confirm that pepper could enhance the bioavailability of drugs was performed in the late 1970's by Atal and coworkers at the Regional Research Laboratory, Jammu-Tawi in India. These experiments revealed that Piper longum co-administered to rats orally with the drugs vasicine and sparteine increased the blood levels of vasicine by 232% and sparteine by more than 100% as compared to control animals who did not receive P. longum.

In subsequent experiments, piperine has been proven to enhance the bioavailability of a number of drugs including rifampicin, phenytoin, propranolol and theophylline. A patent based on the drug bioretentive property of piperine (Indian Patent No. 1232/DEL/89) recommends the use of piperine in combination with drugs to improve their effectiveness. This successful use of piperine to increase bioavailability of certain drugs has created interest in the area of nutrient and food absorption, since nutritional deficiencies due to poor gastrointestinal absorption are an increasing problem in developing countries as well as in Western nations. In developing countries, overall gross malnutrition may be the culprit. However, in Western nations, poor gastrointestinal absorption is increasing due to a larger percentage of elderly people in the population, as well as an increasing incidence of "junk food diets", allergies, gastric ulcers, and chronic yeast infections (Candidiasis). Beta-carotene absorption has been shown to be variable among humans, with some individuals consistently absorbing it well while others do not. Recently, an original bioavailability study showed that a standardized extract of black pepper (Bioperine®), increases gastrointestinal absorption of beta-carotene in humans. Bioperine is 98% pure piperine obtained through a proprietary extraction process, from pepper. A small amount of Bioperine® (5 mg) combined with a formula containing 15 mg of beta-carotene, given as a food supplement once a day, increased almost twofold the blood levels of beta carotene in human volunteers.These results indicate that Bioperine possesses the potential to increase the bioavailability of nutrients as well. Bioperine was effective in increasing nutrient absorption with a dose several times lower than that commonly used to bioenhance blood levels of a drug. Incidentally, the dose of piperine which increased the bioavailability of beta -carotene was several times lower than the estimated amount of piperine consumed daily in the diet by an average individual in the USA. Similar bioavailability enhancement was observed on co-administration of other nutrients including Coenzyme Q1027, L(+)_Selenomethionine, Vitami B6, Vitamin C (with propranolol hydrochloride) and herbal extracts such as Curcumin with Bioperine.

O. Pepper's "hot" taste, "hot" feel, and its thermogenic effect

Almost everyone recognizes that the black pepper sprinkled on their food makes it taste spicy or "hot". The hot flavor is even stronger when the pepper is used fresh. Pepper's heat is no accident—it is a manifestation of the biological activity of some of the phytochemicals found in pepper, most notably piperine. Black and long peppers stimulate the skin as well as the tongue, thus they are also useful for topical application. They have broad antimicrobial, anti-parasitic and insecticidal properties. Peppers have been traditionally used as local anesthetics, but the mechanism of this analgesic (pain-relieving) action has only been recently described. Piperine is thought to be the main phytochemical responsible for the analgesic action of pepper. It is believed that piperine acts in a similar (but not identical) way to another well-known pungent phytochemical, capsaicin, the principal pungent principle found in cayenne peppers (Capsicum annuum). Black and various red peppers, including cayenne, chilli, and paprika, are all spicy but are not related botanically. According to one concept, piperine may deplete sensory nerves of the neurotransmitter called "Substance P".This action may cause local desensitization to pain stimuli. It has been proposed that Bioperine acts through thermoreceptors, both locally in the skin nerve endings, and systemically, throughout the nervous system. This, in turn, interferes with pain stimulus transmission and causes desensitization of pain receptors. The proposed mechanism through thermoreceptors, which are sensors of heat energy in the body, may shed light on the thermogenic (heat-generating) action of pepper and piperine. The thermogenic effect of piperine and other components of spices such as capsaicin, gingerol and shogaol is now broadly discussed as a new application of spices traditionally known for their body temperature regulating properties. Thermogenesis is now scientifically linked to body metabolism and the metabolic rate. The higher the metabolic rate, the more heat energy is being produced by the body. Could it be that thermoregulation by piperine is a mechanism through which metabolism can be regulated, including the metabolization of nutrients and drugs? Considering the profound effects of piperine on nutrient absorption when given orally in a dose as small as a few milligrams, piperine deserves to be called a "super nutrient" and based on its possible thermogenic effect on the body, it might also be dubbed a "thermonutrient". Although the concept of thermogenesis was not recognized in Ayurvedic medicine, there existed an empirical use of certain combinations of herbs and minerals specifically targeted to improve the digestibility of food. Traditionally, black pepper and its close relative long pepper are used in combination with ginger in trikatu (three acrids), a remedy used for a broad range of gastrointestinal disorders. The sharp-tasting principles in trikatu are used to increase the protective gastrointestinal mucous secretion, a long-standing Ayurvedic treatment which has proven successful for both acute and chronic gastrointestinal conditions. Indeed, recent experimental evidence shows that piperine has anti-inflammatory and antioxidant properties. Piperine may facilitate nutrient absorption by alleviating inflammatory conditions at the site of absorption. The mechanisms behind the beneficial action of piperine as one of the principal ingredients of numerous digestive formulas employed by Ayurveda needs to be further investigated. Particular emphasis needs to be placed on the traditional sense of restoring gastrointestinal function as means of preventing disease and improving overall nutrition. Black pepper and long pepper are thus potentially useful herbs in the management of a variety of respiratory and gastrointestinal problems. Future research on pepper may well retrace the origin and evolution of the properties which attracted attention to pepper in ancient times. Pliny commented some 2,000 years ago: "it is quite surprising that the use of pepper has come so much in fashion, its only desirable quality being a certain pungency; and yet it is for this that we import it all the way from India!". This pungency of pepper is now understood to be a byproduct of the biological properties of piperine, which can apparently regulate neurohormones, thereby increasing thermogenesis, or the production of heat by the body. Scientific research has now revealed that the "hot" pepper taste is due to the production of heat energy. The biological mechanism of piperine is strongly linked to its hot taste, further validating its representation as 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 BLACK PEPPER ESSENTIAL OIL (BPEO) AND PIPERINE

The piperine, BPEO and its active constituents have a number of potential biological activities, including antioxidant, antimicrobial, antitumor, cytotoxicity, and miscellaneous activities.

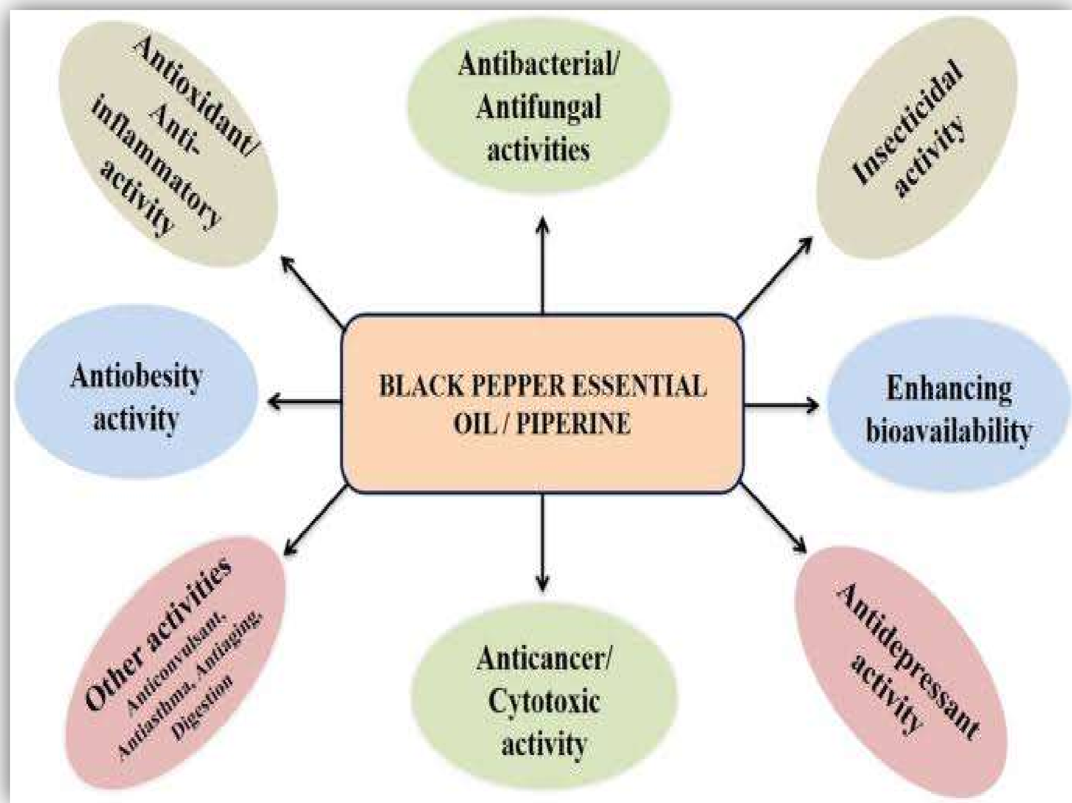

Figure 8: Pharmacological activities of pepper

Piperine is a compound belonging to the alkaloids; it is responsible for the pungent taste of various pepper species, and has, in addition to being found in the members of the Piperaceae family, been detected in several other plant species (Rhododendron faurie, Vicoa indica, Anethum sowa, and others). The amount of piperine is highest in Piper nigrum L., and varies from 2% to as high as 9% , depending on environmental factors such as climate and/or place of origin, as well as growing conditions. Black pepper (Piper nigrum L.) is the most used among the pepper species, and along with its worldwide utilization as a spice, it is known as an important medicinal plant. Its traditional use can be traced to thousands of years ago, due to its unique role in Ayurvedic medicine, where it represents one of the components of "tricatu" (equal proportions of black pepper, long pepper and ginger). Tricatu or its individual compounds are the base for 210 out of 370 formulations listed in the Handbook of Domestic Medicines and Common Ayurvedic Remedies. Pepper is traditionally recommended for fevers and a variety of gastrointestinal conditions, as well as for neurological and broncho-pulmonary disorders (asthma and chronic bronchitis). Traditional medicine, such as Chinese medicine, utilizes black pepper for the treatment of various pains (headaches, muscular pain), rheumatism, infections such as strep throat and influenza, as well as for enhancing the blood circulation. Pepper contains fibers, starch, proteins, carbohydrates, lignans, alkaloids, flavonoids, phenols, amides and essential oil. The compounds that are found in black pepper essential oil, which is present in a content of up to 3.5% in the fruits, give it a specific aroma and taste. The major compounds found in this essential oil are sabinene, α-pinene and β-pinene, β-caryophyllene, phellandrene, limonene, linalool, citral and others. Among other compounds, antioxidants such as beta carotene, lauric, myristic and palmitic acids, as well as piperine, are found in pepper. The pungent taste of pepper and its many pharmacological properties are attributed to piperine (piperoylpiperidine, $C_{17}H_{19}NO_3$), one of its major alkaloids. Investigations on piperine bioactivities have reported the very high spectrum of physiological effects, including antihypertensive, antiaggregant, antioxidant, antitumor, antispasmodic, antiasthmatic, antidepressant, anxiolytic, and many others. Along with an array of biological activities, piperine is known for its ability to increase the bioavailability of drugs, and thus enhance their therapeutic potential. Along with beneficial effects, piperine has, as the main ingredient of the most known spice, pepper, been traditionally used as a food for centuries, and does not present any threat upon human consumption. Additional studies have revealed the safety of its consumption by reporting a lack of piperine genotoxicity in Ames tests and in micronucleus tests. This review encompasses the available literature data on the various biological activities of piperine, as well as the results of clinical studies performed on humans.

A. Antioxidant effects

Oxidative stress is the main factor for initiation of various degenerative and chronic diseases, including cancer,immune dysfunction, diabetes and Parkinson's Antioxidants are natural or synthetic constituents that canbe used for inhibition of free radical formation by scavenging and suppression of degenerative and chronic diseases.A polyphenolic compound Hydroxytyrosol(HT), has a potent antioxidant effect on hydrogen donation and improved radical stability .Supplementation with HT improves the white adipose tissue (WAT)dysfunction induced by high-fat diet (HDF) fed in mice through the modulation of transcription factors NF-κB,Nrf2, SREBP-1c and PPAR-γ as well as their target genes, involved in inflammation, antioxidant defences and lipogenesis .Vijayakumar et al. Noted that piperine has potential protection activity againstlipid peroxidation and antioxidant activity in rats fed a high-fat diet which induced oxidative stress to cells. Piperine has greatest antioxidant potential and was utmost effective with minimum inhibitory concentration (MIC) < 325 mg/ml against all assessed gram positive and negative strains. Under invitro conditions, Jeena et al. recorded that essential oil of black pepper scavenged superoxide, and inhibited tissue lipid peroxidation.

B. Antibacterial and antimicrobial effects

In general, consumers prefer natural and non-toxic products to protect foods from bacteria during storage. Because of the long-term usage of chemical preservatives, a resurgence of food pathogenic bacteria may occur, which can induce severe health problems in humans. The antimicrobial activity of black pepper remains unclear till date. Piperine had potential antimicrobial as well as antifungal effects against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Aspergillus Niger, (A) flavus, Alternaria alternata and Fusarium oxysporum. Phenolic compounds obtained from fresh black pepper seed extractshave the potential to inhibit the growth of Bacillus, Escherichia coli and Staphylococcus aureus, S. faecalisand (B) cereus. Zhang et al. showed that 1.0 µl/ml of BPEO was the effective minimum inhibition concentration against meat-borne E. coli, and suggested that black pepper essential oil has potential as a natural antibacterial agent in the meat industry. Similarly, BPEO displayed substantial activity against E. coli, B. substilis, and S. aureus.

C. Anticancer effects

The BPEO and piperine exert activities against several types of cancer. Piperine significantly suppressed the tumour growth of both androgen-dependent and androgen-independent prostate cancer cells. Makhov et al noted enhanced anticancer activity during co-administration of piperine and docetaxel in human prostate cancer. Additionally, piperine induced DNA damage and apoptosis in tumour cells and was a potential therapeutic agent for the treatment of osteosarcoma. Likewise, piperine reduced lung cancer by stimulation of antioxidative protective enzymes and through reducing lipid peroxidation. Based on the above comments, piperine has potential anticancer activities. However, only a few studies have studied the antitumor potential of piperine and BPEO, and these were conducted in animal models only. Therefore, futurestudies should be attentive on the bioactivity of BPEO in several clinical investigations with humans.

Breast Cancer: The study on HER2 overexpressing breast cancer cells demonstrated inhibited proliferation and induced apoptosis by activating caspase-3 and cleavage of PARP. Moreover, it was determined that piperine inhibits HER2 gene expression at the transcriptional level and enhances sensitization of HER2 overexpressing cells to paclitaxel killing. The same study found that it inhibits AP-1 and NF-κB activation, blocks extracellular signal-regulated kinase (ERK1/2), p38 mitogen-activated protein kinase (p38 MAPK), and Akt signaling pathways, and suppresses epidermal growthy factor (EGF)-induced MMP-9 expression. Without affecting normal mammary epithelial cell growth, piperine inhibits the in vitro growth of triple-negative breast cancer cells (TNBC), and hormone-dependent breast cancer cells. Also, it increases the expression of p21(Waf1/Cip1) and inhibits survival-promoting Akt activation, inhibits mammosphere formation, breast stem cell marker aldehyde dehydrogenase (ALDH), and Wnt signaling pathway without causing toxicity to differentiated cells . In another study, on TNBC cells, the efficacy of factor-related apoptosis-inducing ligand (TRAIL)-based therapy has been enhanced when piperine was added as an adjuvant. In a model of 4T1 murine breast cancer cells, injection of piperine into tumors (35–280 µmol/L) inhibited the growth of 4T1 cells in a time- and dose-dependent manner, and decreased the expression of MMP-9 and MMP-13 . It has been reported that piperine analogs, formed by replacing the piperidine nucleus with different amino acids and substituted aniline, exhibit significantly enhanced activity against human breast cancer cells. The best cytotoxic activity (IC50—0.74 µmol) was obtained by a histidine analog of piperine containing imidazole ring structure

Lung Cancer: A set of studies investigated the effect of piperine on lung cancer and found very promising results. Lin et al found that piperine showed selective cytotoxicity toward lung cancer cell line (A549) by inducing apoptosis through arresting G2/M phase of the cell cycle and activating caspase-3 and caspase-9 cascades in cancer cells. It also decreased Bcl-2 protein expression and increased Bax protein, leading to higher Bax/Bcl-2 ratio. Benzo(a)pyrene induces lung carcinogenesis, by decreasing glutathione transferase (GST), quinone reductase (QR) and UDP-GT and increasing the hydrogen peroxide level. In the study on Swiss albino mice, piperine (50 mg/kg b.wt.) was orally given to mice together with benzo(a)pyrene (BaP) for 16 weeks. In animals treated with piperine, reduced levels of lipid peroxidation, protein carbonyls, nucleic acid content, and polyamine synthesis were recorded in comparison to the control groups, which demonstrated BaP-induced lung carcinogenesis-protective effect of this compound. Piperine exerts BaP-induced cytotoxicity in

V-79 lung fibroblast cells, due to a decrease in GST and UDP-GT . Administration of piperine reduces DNA damage and DNA-protein cross-links in the lung cancer-bearing animals. In this study, mitochondrial enzymes (isocitrate dehydrogenase (ICDH), ketoglutarate dehydrogenase (KDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH)), glutathione-metabolizing enzymes GPx, GR and glucose-6-phospho dehydrogenase(G6PDH) were significantly reduced, while NADPH-cytochrome reductase (NADPH-C reductase), cytochrome P450 (cyt-p450) and cytochrome b5(cyt-b5) showed increased levels in mice administered with piperine. Also, in these animals, ATPase enzymes in erythrocyte membrane and tissues were shown to be increased, while sodium/potassium/magnesium ATPase enzyme activities decreased, showing the chemopreventive effect of piperine . Lung metastasis in C57BL/6 mice , 4270 of 29 induced by B16F-10 melanoma cells has been significantly inhibited when piperine was co-administered together with tumor induction. The results showed reduced lung collagen hydroxyproline, uronic acid, and hexosamine content, a significant decrease in tumor nodule formation and lung size and also a reduced serum sialic acid and serum È-glutamyl transpeptidase activity, pointing to very promising antimetastatic activity of piperine.

Prostate Cancer: When investigating the effect of piperine to voltage-gated K+ channels (KV), which play an important role in regulating cancer cell proliferation and are considered as potential targets for the treatment of cancer, it was found that it blocks voltage-gated K+ current. It was effective in doses of IC50 = 39.91 µM in LNCaP and 49.45 µM in PC-3 human prostate cancer cells. This recorded blockade led to G0/G1 cell cycle arrest and consequently inhibited cell proliferation and induced apoptosis. In another study, on human prostate cancer DU145, PC-3 and LNCaP cells, piperine was also found to induce cell cycle arrest at G0/G1, and to cause downregulation of cyclin D1 and cyclin A, while increased levels of p21Cip1 and p27Kip1 were found upon the piperine treatment in prostate cancer cells (LNCaP and DU145). Additionally, piperine treatment resulted in promoted autophagy as evidenced by the increased level of LC3B-II and the formation of LC3B puncta. In LNCaP, PC-3, and DU-145 prostate cancer cells, piperine activated caspase-3 and cleaved PARP-1 proteins and reduced the expression of phosphorylated STAT-3 and NF-kB transcription factors. A recent study determined that molecular mechanism responsible for observed repressed cell proliferation and migration (in PCa DU145 cell line) of piperine action was via affecting the expression of the Akt/mTOR/MMP-9 signaling pathway. Cervical and Ovarian Cancer Piperine and mitomycin-C (MMC) co-treatment resulted in inactivating STAT3/NF-κB, leading to suppression of the Bcl-2 signaling pathway in human cervical cancer. Also, this compound, together with its analogs demonstrated significant potential against Hela cervix cell line. A recent study showed that piperine (8, 16, and 20 µM) inhibited cell viability and caused apoptosis in human ovarian A2780 cells via JNK/p38 MAPK-mediated intrinsic apoptotic pathway . Further analysis on the mechanism of its action demonstrated increased levels of cyt-c from mitochondria and consequently increased caspase (caspase-3 and -9) activities and also decreased phosphorylation of JNK and p38 MAPK following piperin treatment.

Cancers of the Gastrointestinal Tract: Piperine significantly increased the levels of lipid peroxidation in 7,12-dimethyl benz [a] anthracene (DMBA)-induced hamster buccal pouch carcinogenesis. This chemopreventive efficacy of piperine was recorded by FT-IR spectroscopic technique, where decreased levels of proteins and nucleic acid content were found in comparison to untreated cancer cells. In AGS human gastric cancer cells, piperine decreases Bcl-2, XIAP (anti-apoptotic), and Akt, while p53, Bax (pro-apoptotic), cleaved caspase-9, and cleaved-PARP increased. Piperine inhibits IL-1 β-induced p38 MAPK and STAT3 activation and, in turn, blocks the IL-1 β-induced IL-6 expression in TMK-1 gastric cancer cells. It also decreases the protein levels of Bcl-2, Mcl-1, survivin, and increases the Fas levels, resulting in inhibition of the growth of HT-29, human colon cancer cells. In HT-29 colon carcinoma cells, piperine reduces the levels of cyclins (D1 and D3), cyclin-dependent kinases (CDK-4 and 6), and upregulates p21/WAF1 and p27/KIP1 expression. The study of Yaffe et al. found that this natural compound inhibited the growth of HRT-18 human rectal adenocarcinoma cells by causing apoptosis. The same study found that this effect has been at least partially caused by creating increased production of reactive oxygen species (ROS) in the cancer cells treated with piperine. The activation of the mechanistic target of the rapamycin complex 1 (mTORC1) was found to be associated with sustained inflammation and, the progression of colorectal cancer. Piperine alone and in combination with curcumin plays a preventive role in the development of colorectal cancer by inhibiting TNF-α and mTORC1 in human intestinal epithelial cells .

Other Cancer Types: Piperine inhibits PKCα and ERK phosphorylation and reduces NF-κB and AP-1 activation, leading to down-regulation of MMP-9 expression in human fibrosarcoma HT-1080 cells. In B16F10 melanoma cells, piperine (2.5, 5 and 10 µg/mL) inhibited activation of transcription factors NF-κB, c-Fos, cAMP response element-binding protein (CREB), activated transcription factor (ATF-2) and consequently downregulated inflammatory and growth regulatory genes IL-1β, IL-6, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF). In ultraviolet-B-irradiated mouse melanoma cells (B16F10), piperine promotes cell death through the elevation of intracellular ROS formation, calcium homeostasis imbalance, and loss of mitochondrial membrane potential. Synthetic piperine–amino acid ester conjugates exhibit cytotoxic activities against IMR-32, MCF-7, PC-3, DU-145, Colo-205, and Hep-2 cancer human cell lines

D. **Cytotoxicity effects**

BPEO and piperine have good potential for augmenting the effectiveness of tumour necrosis factor (TNF) related apoptosis in breast cancer cell. Greenshields et al.reported that a combination of piperine and γ-radiation had higher cytotoxicity and effectiveness in stopping the growth of tripe negative cancer cells than radiation alone in immune-deficient mice. Although the safety of piperine and BPEO was showed, the use of cell lines only on in vitro assays confines the therapeutically relevance of this outcome.

E. **Insecticidal effects**

Black pepper possesses insecticidal activities against European chafer (Amphimallon majale, Coleoptera:Scarabaeidae) Upadhyay and Jaiswal noticedthat 0.2 % concentration (v:v) of black pepper essential oil has potential repellent activity against adults of the major wheat grain storage pest Tribolium castaneum (Herbst). Naseem and Khan stated that a higherconcentration of black pepper essential oil leads to maximum repellent effects at maximum exposure duration against T. castaneum. Thus far, only two studies have investigated the insecticidal effects of BPEO; therefore, further research needed in this promising application.

F. Anti-inflammatory effect

Inflammation is complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants and anit-inflammatory means something which reduces the human body inflammation and black pepper is one of such substance. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids which affect the central nervous system. Antiinflammatory drugs used for treating chronic inflammatory diseases such as rheumatoid arthritis are typically prescribed long term to properly control the disordered immune system. It is found that piperine significantly inhibited the production of two important proinflammatory mediators, IL6 and PGE2, in IL1β-stimulated human FLS. The inhibition of PGE2 production is important due to its central role in triggering pain. In addition, MMP1 and MMP13 collagenases play dominant roles in RA and osteoarthritis because they are the rate-limiting components of the collagen degradation process. The significant inhibition of MMP13 expression is particularly important because it degrades a wide range of collagenous and non-collagenous extracellular matrix macromolecules and is remarkably active against collagen type II, the predominant collagen in cartilage. Piperine inhibits the expression of MMP13 in IL1β-stimulated FLSs. Piperine showed a significant inhibition of increase in oedema volume in a carragenin induced test. Piperine acted significantly on early acute changes in inflammatory process.

G. Antireproductive Activity

Srivastava et al.reported that the antireproductive activity of piperine against the snail Lymnaea acuminata and observed that piperine caused a significant reduction in the fecundity, hatchability and survival of the snail Lymnaea acuminata in each month of the year Nov. 2011 to Oct. 2012. Treatment with the piperine also prolong the hatching time of snails. Sublethal treatment ofpiperine caused a significant ($p<0.05$) reduction in protein, amino acids, DNA, RNA and AChE in the ovotestis/nervous tissue of treated snails with respect to control after 96h exposure period. Simultaneously, inhibition in acetylcholinesterase (AChE) activity in nervous tissue was also noted. The active component piperine (Piper nigrum) is an effective molluscicide against L. acuminata. Constituent of piperine in vitro inhibit enzyme activity which is responsible for leukotriene and prostaglandin biosynthesis; 5-lipoxygenase and COX-1The cerebral neurosecretory caudo dorsal cells (CDCS) of the fresh water pulmonate snail Lymnaea stagnalis control egg lying, an event that involves a pattern of stereotyped behavior .The CDCS synthesize and release multiple peptides, among which is the ovulation hormone (CDCS). It is thought that each peptide controls a specific aspect of the processes involved in egg laying. The synthesis of protein in any of a tissue can be affected in two ways by a chemical, it either affects the RNA synthesis at the transcription stage or it somehow affects the uptake of amino acids in the polypeptide chain. Both these possibilities may account for the lower protein content in the affected tissue. In the first case, the RNA synthesis would be inhibited resulting in reduced RNA as well protein content. In the second case, only the protein content would be affected. Piperine inhibits P-glycoprotein and the major drug metabolizing enzyme CYP3A4. It seems that cumulative effect of molluscicide piperine on the level of protein, amino acids and nucleic acids in ovotestis of L. acuminata directly/or indirectly DCs, which release ovulation hormone and ultimately affect the reproduction of snails in each month of the year. The AChE activity is one of the biomarker most frequently used in ecotoxicology. The enzyme is responsible for the breakdown of ACh in cholinergic synapses, preventing continuous nerve firing, which is vital for normal cellular neurotransmitter functioning. The AChE inhibition result in accumulation of acetylcholinesterase at the nerve synapses so that the post synaptic membrane is in a state of permanent stimulation producing paralysis, ataxia and general lack of coordination in neuromuscular system and eventual deathdeath.

H. Analgesic and anticonvulsant

The interest in the exploration for novel and safe pain-alleviating natural agents has stimulated scientists to study P. nigrum as a therapeutic pain agent. determined the analgesic activity of hexane and ethanolic extracts of P. nigrum and its compound piperine using the tail immersion, analgesy-meter, hot-plate, and acetic acid induced writhing test. In the tail immersion method, piperine showed the maximum analgesic effect after 120 min at a dose of 5 mg/kg (reaction time by mice to withdraw the tail11.658 s) while in the analgesy-meter test, the ethanolextract was most effective after 60 min dose of 10 mg/kg (reaction time ¼ 20.900 s). The highest reaction time for paw licking or jumping in the hot plate method was exhibited by piperine (12.870 s after 30 min at a dose of 10 mg/kg). In the writhing test, piperine (dose of 10 mg/kg) and the ethanol extract (dose of 15 mg/kg) completely stopped the number of writhes in mice induced by acetic acid. Additionally, the anticonvulsant effect of P. nigrum was also studied. Belemkar, Kumar, and Pata (2013) observed that the ethyl alcohol and hexane extract of P. nigrum suppressed the onset and duration of seizures in Wistar rats using both pentylenetetrazol (PTZ) induced model and maximal electroshock seizure (MES) induced model. In addition, Bukhari et al. (2013) found that 50 mg/kg piperine treatment was most effective than 70 mg/kg in preventing the animals from PTZ-induced seizures. The highest tested dose of piperine (70 mg/kg) increased the latency of picrotoxininduced convulsions to 878.5 s compared to the value of control group 358.4 s. Hypoglycemic and hypolipidemic Treatment of diabetic rats with P. nigrum aqueous seed extract for 4 weeks reduced the blood glucose level to 129 mg/100 mL compared to diabetic rats (270 mg/100 mL) (Kaleem, Sheema, Sarmad, and Bano 2005). 100, 200, and 300 mg/kg body weight of the leaf methanolic extract of P. nigrum reduced blood glucose level in alloxan induced diabetic rats after 21 days of treatment (Onyesife, Ogugua, and Anaduaka 2014). Aldose reductase is primarily involved in the development of long-term diabetic complications due to increased polyol pathway activity, therefore, its pharmacological inhibition has been recognized as an important strategy in the prevention and attenuation of associated complications particularly retinopathy, neuropathy, and nephropathy. Indeed, the study by Gupta, Singh, and Jaggi 2014b observed that the hydromethanolic extract of the seed inhibited goat lens aldose reductase, with an IC50 value of 35.64 lg/mL. Supplementing piperine to the high fat diet rats lowered the levels of plasma total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), HMG CoA reductase and raised the level of lipoprotein lipase (LPL) and lecithin-cholesterol acyltransferase (LCAT) compared to rats which did not receive piperine.

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

Healthy gut microbiota helps to increase the immune system of COVID-19 patients.there is unmet need to identify the different microbial metabolites present after the degradation of piperine and other plant-derived molecules by using LC–MS/MS. Microbial metabolites have an ability to cross the BBB and provide pleiotropic effects on the brain and other organs by altering the gene expression. Healthy gut microbiome identification in stool samples of COVID-19 patients may be a better approach for precision medicine by utilizing Fecal Micro-biota Transplantation (FMT) technologies for COVID-19 patients. Black pepper consumption, besides its immu-nomodulatory functions, may also aid in combating SARS-CoV-2 directly through possible antiviral effects. It has recently been reported that piperine has demonstrated binding interactions toward the spike gly-coprotein and ACE2 cellular receptor for SARS-CoV-2. interactions of hydrogen bonds with Gly399, His401, Glu402, Arg514, Arg518 were found significant by forming one predictable hydrogen bond with each amino acid residue. Piperine interacts with the main pro-tease at the docking score of -90.95 and binding energy score of -78.10kcal mol−1, forming one hydrogen bond with His41; other stabilizing interactions include π -sul-fur, π–σ, π–π T-shaped, and alkyl interactions. Piperine with a binding affinity of −6.4kcalmol−1 forms hydrogen bond interaction with GLY164 and GLY170; its binding process is also governed by van der Waals interactions with ARG71, TYR121 (TYR453), TYR163 (TYR495), and ASN169 (ASN501) of SARS-CoV-2 receptor-binding domain spike protein (RBD Spro). The major stabiliz-ing interactions of piperine with SARS-CoV-2 RBD Spro were by covalent hydrogen bonding, π–π T-shaped, and van der Waals force of interactions. Piperine acts on the Nsp15 viral protein and inhibits SARS-CoV-2 replication. Furthermore, binding chemistry of piperine and curcumin via π–π intermolecular inter-actions enhances curcumin's bioavailability, which facilitates curcumin to bind RBD Spro and ACE-2 receptors of host cell, thereby inhibiting the entry of virus.

J. Enzyme-Related Activity

Monoamine Oxidase Activity Piperine exhibits antidepressant-like effects by regulating the monoaminergic system. The biochemical method of measuring the monoaminergic system is by monoamine oxidase (MAO) content, and piperine was found to inhibits this enzyme. The IC50 values for MAO-A and B reduction by piperine were 20.9 and 7.0 µM, respectively. Not only piperine, its related structures methylpiperate, guineensine, and piperlonguminine, or its derivative antiepilepsirine exhibited a similar effect. In combination with ferulic acid, piperine exhibits a synergetic effect on MAO inhibition. Other Enzymes Piperine decreases cyt-P-450, benzphetamine N-demethylase, aminopyrine N-demethylase, and aniline hydroxylase activities . Also, the basal activity of TWIK-related acid-sensitive K+ channel (TASK-1, -3), and TWIK-related spinal cord K+ (TRESK) channels were inhibited by piperine in a dose-dependent manner. It activates transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor, a novel anti-epileptogenic target, indicating the anti-seizure effects. Chen et al. recently reported the effects of piperine (5 and 10 mg/kg) on the testis development in the pubertal rat, where piperine increased the ratio of phospho-AKT1 (pAKT1)/AKT1, phospho-AKT2 (pAKT2)/AKT2, and phospho-ERK1/2 (pERK1/2)/ERK1/2 in the testis in rats, showing a stimulating effect to the Leydig cell development. Piperine increases GABA levels and inhibits neuronal NOS, leading to antianxiety activity in stressed mice. Investigation of its effect on microsomal P450s showed diverse action, where P4501A and P4502B increased, and P4502E1 expression was suppressed in animals treated with piperine. Acute acetaminophen poisoning results in increased AST and ALT levels in hepatotoxic rats. Pretreatment with piperine prevents the increased levels of these enzymes. In the study which investigated the free radical scavenging properties of piperine in rat intestinal lumen model (exposed to hydrogen peroxide and cumene hydroperoxide), piperine significantly increased GSH level. In MC3T3-E1 cells, piperine increases osteoblast differentiation through AMPK phosphorylation, by inhibiting of DNA binding-1, and runt-related transcription factor 2 (Runx2). Piperine inhibits phorbol 12-myristate 13-acetate (PMA)—induced NF-κB, C/EBP, and c-Jun nuclear translocation, inhibits activation of the Akt and ERK, leading to inhibition of cyclooxygenase-2 expression in murine macrophages, and suppresses T cell activity and Th2 cytokine production in the ovalbumin-induced asthmatic mice. In pilocarpine-induced epileptic rats, piperine exhibits anticonvulsant activity by upregulating caspase 3 and decreasing Bax/Bcl 2 . Piperine lowers the serum levels of thyroxin, triiodothyronine and glucose concentrations while decreasing hepatic 50D enzyme and glucose-6-phosphatase in adult male Swiss albino mice. The enzyme activities are on par with a standard antithyroid drug, propylthiouracil. Piperine inhibits two carbonic anhydrases (CAs), human cytosolic isoforms hCA I and II . These enzymes catalyze a physiological reaction of the conversion of CO2 to the bicarbonate ion and protons and are involved in many physiological and pathological processes including carcinogenesis. Discovery of inhibitory activity of piperine against CAs shows its potential as an anti-convulsant, analgesic, anti-tumor, and anti-obesity agent.

K. Immunomodulatory and Anti-Allergic Effect

The immunomodulatory potential of piperine have demonstrated promising potential. Bezerra et al. reported that the incubation of tumor cell lines with 5-fluorouracil (5-FU) in the presence of piperine produced an increase in growth inhibition, observed by lower IC50 values for 5-FU. At the same time, leucopoenia induced by treatment with 5-FU was reduced by the combined use with piperine, showing improved immunocompetence hampered by 5-FU. In the study of Bernardo et al., which evaluated the effect of piperine to B cell functioning and on the humoral immune response to T-un/dependent antigens, it was found that, in vitro, it inhibits proliferative response induced by lipopolysaccharide (LPS) and immunoglobulin α-IgM antibody. Also, piperine resulted in inhibition of IgM antibody secretion and reduced expression of cluster of differentiation CD86. A recent study of Lee et al. demonstrated that piperine in combination with gamma-aminobutyric acid (GABA) mediated p38 and JNK MAPK activation, which increased EPO and EPO-R expression, resulting in up-regulation of IL-10 and NF-κB . In addition to immunomodulation, piperine exhibits significant anti-allergic activity in ovalbumin-induced allergic rhinitis in mice. Piperine significantly ameliorated sneezing, rubbing, and redness induced by sensitization of nerve endings resulted from histamine released in response to antigen-antibody reaction , but also decreased nitric oxide (NO) levels due to lower migration of eosinophils into nasal epithelial tissue. 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

Piperine increases the cell viability and restored mitochondrial functioning and primary neurons in rotenone-induced neurotoxicity in SK-N-SH cells. It also inhibits mTORC1 and activates protein phosphatase 2A, leading to neuroprotective effects in Parkinson's disease model. This compound exerts protective effects against neurotoxicity induced by corticosterone (PC12 Cells) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Also, piperine exhibits the neuroprotective effect on primarily cultured hippocampal neuron and suppresses the neurite extension in developing neurons. In rats with streptozotocin (STZ)-induced experimental dementia of the Alzheimer's type, intraperitoneal administration of piperine (2.5, 5, and 10 mg/kg), vehicle, and memantine (10 mg/kg) for two weeks after the first STZ administration resulted with cognitive-enhancing effect. The results of cognitive function were consistent with a reduced level of malondialdehyde in cerebrospinal fluid (CSF) and hippocampus (HC) of the treated rats. Based on the described results, the cognitive-enhancing effect of piperine was attributed to its positive effects on the redox balance of CSF and HC neurons. In a pilocarpine-induced rat model of epilepsy, administration of piperine reduced oxidative stress and inflammation and ameliorated memory impairment. Piperine alone was found to produce a weak antidepressant-like effect in the tail suspension and forced swimming tests, while in combination with trans-resveratrol (tR) it enhanced its antidepressive action. Further testing indicated that the effect of tR and piperine on depressive-like behaviors might be partly due to the potentiated activation of monoaminergic system in the brain. Similar results were found in several other studies on piperine alone, in combination with ferulic acid, and its various derivatives. Piperine relieves the depression in chronic unpredictable mild stress rats by modulating the function of the hypothalamic-pituitary-adrenal axis. Piperine was found to possess analgesic and anticonvulsant effects, where intraperitoneal (i.p.) administration of piperine (30, 50 and 70 mg/kg) significantly inhibited the acetic acid-induced writhing in mice, while tail-flick assay resulted in prolonged reaction time of mice at doses of 30 and 50 mg/kg. The anticonvulsant effect of piperine has been demonstrated through delayed onset of pentylenetetrazole- and picrotoxin-induced seizures in mice. These anti-seizure effects of piperine were found to be related to transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors. Another study reported analgesic activity of piperine, where hot plate reaction test and acetic acid test were used and confirmed analgesic efficacy of intraperitoneally administered piperine

M. Miscellaneous effects

For centuries, black pepper has been used for traditional medicines to cure cuts and wound injuries. Piperine induced bioavailability of the flavonoid linarin in rats by inhibiting the P-glycoprotein, and it helps cellular efflux during intestinal absorption. Hence, piperine is called a natural bio-enhancer. Piperine stimulates a dose-dependent increase in the secretion of gastric acid and interruption of gastrointestinal motility. The oral administration of piperine activates the liver, pancreas and digestive enzymes in the small intestinal mucosa. Furthermore, the addition of piperine in foodmaterials as food flavours may increase the protease, lipase, and pancreatic amylase activities.

Negative Aspects of Piperine: At high doses, piperine is acutely toxic to mice, rats, and hamsters. The LD50 values for a single i.v., i.p., s.c., i.g. and i.m. administration of piperine to adult male mice were 15.1, 43, 200, 330, and 400 mg/kg body wt, respectively. Considering oral application, LD50 values were shown to be 330 mg/kg in mice and 514 mg/kg in rats. Piperine increases serum aspartate aminotransferase and ALP, while total serum protein decreased, which results in considerable damage to the liver in CF-1 albino mice. Administration of piperine enhances the aflatoxin B1 binding to calf thymus DNA in vivo in rat tissues. In the study of D'cruz and Mathur, which studied the effect of piperine on the epididymal antioxidant system of adult male rats, a negative effect was recorded throuh reduced weights of the caput, corpus and cauda regions of the epididymis. Also, the results pointed to decreased sperm count, motility and viability, decreased levels of sialic acid and also a decrease in the activity of antioxidant enzymes at a dose of 100 mg/kg. Therefore, due to increased ROS levels in the epididymis, sperm function can be damaged by intake of piperine. Similar effects of piperine were recently reported for pubertal rats administered with piperine (5 and 10 mg/kg) for 30 days. In the mentioned study, piperine increased testosterone (T) and follicle-stimulating hormone (FSH) levels, number and size of Leydig cells, but negatively affected spermatogenesis. This was partially opposite to the results of the earlier study, which reported only negative effects of piperine to testes, and performed the same treatment of mature male albino rats (administered for 30 days at the same doses of 5 and 10 mg/kg). The results of this study showed that lower dose caused partial degeneration of germ cell types, while a higher dose, on the other hand, caused severe damage to the seminiferous tubule, a fall in caput and cauda epididymal sperm concentrations, decrease in seminiferous tubular and Leydig cell nuclear diameter and desquamation of spermatocytes and spermatids. In these, piperine treated rats, an increase in serum gonadotropins, and a decrease of intratesticular T concentration were reported as well.

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. So, the plant needs more experimental and clinical studies to investigate the mechanism of action of the plant extracts in the animal body to prove the significant effects of the plant in treating various diseases.

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