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A REVIEW ON DIVERSIFIED USE OF THE KING OF SPICES: *PIPER NIGRUM* (BLACK PEPPER)

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ABSTRACT: Black pepper, the 'King of spices' (*Piper nigrum* L.), is a widely used spice, known for its pungent odour. From time immemorial, plant sources were used in traditional systems of medicine and day-to-day common use, such as in meal preparation and cosmetic purposes. This is due to their vast pharmacological potential with minimum side effects. Among the various species of the Piperaceae family, black pepper is one of the most popular due to its principle pharmacological component, piperine. Which is an alkaloid that has diverse pharmacological activities like antioxidant, anti-obesity, antitumor, antipyretic, anticonvulsant, anti-thyroid, antifungal, antibacterial, insecticidal, hepatoprotective, anti-asthmatic, larvicidal, antihypertensive, anti-inflammatory, antidiabetic, antidiarrheal, bio-availability enhancer, immunomodulator, antiepileptic, antifertility, GI stimulant, lipid metabolism accelerator, anticancer, CNS stimulant, diuretic, aphrodisiac, blood purifier and antiplatelet activities, *etc*. Due to some religious value of black pepper, its being popular from ancient time to modern generation. This review is aimed to provide a literature review on recent advancement of chemistry, pharmacognosy, pharmacological activities, new piperine based formulations and other general use of *Piper nigrum*.

INTRODUCTION: *Piper nigrum* belongs to the family Piperaceae, it is a perennial shrub native to southern India, and has been extensively cultivated there and in other tropical regions.

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As of 2013, Vietnam is the world's largest producer, as well as exporter, of pepper, producing 34% of the global *P. nigrum* crop. Due to its strong pungency, it is regarded as the 'King of spices' and it has valuable medicinal potency.

It is one of the world most common kitchen spices and well known for its pungent chemical constituent piperine (1-peperoyl piperidine, **Fig. 2**), discovered in 1819 by Hans Christian, which has diverse pharmacological activities. It is commonly known as Kali mirch in Urdu and Hindi, Marich in

Nepali, Pippali in Sanskrit, Milagu in Tamil, and Black Pepper, Peppercorn, Green pepper, White pepper, Madagascar pepper in English [1, 2]. It is widely accepted and most used in different traditional systems of medicine, like the Unani and Ayurvedic systems [4].

FIG. 1: HARVESTED BLACK PEPPER SEEDS (L.) AND PEPPER FRUIT (GREEN AND RIPENING PINK YELLOW)

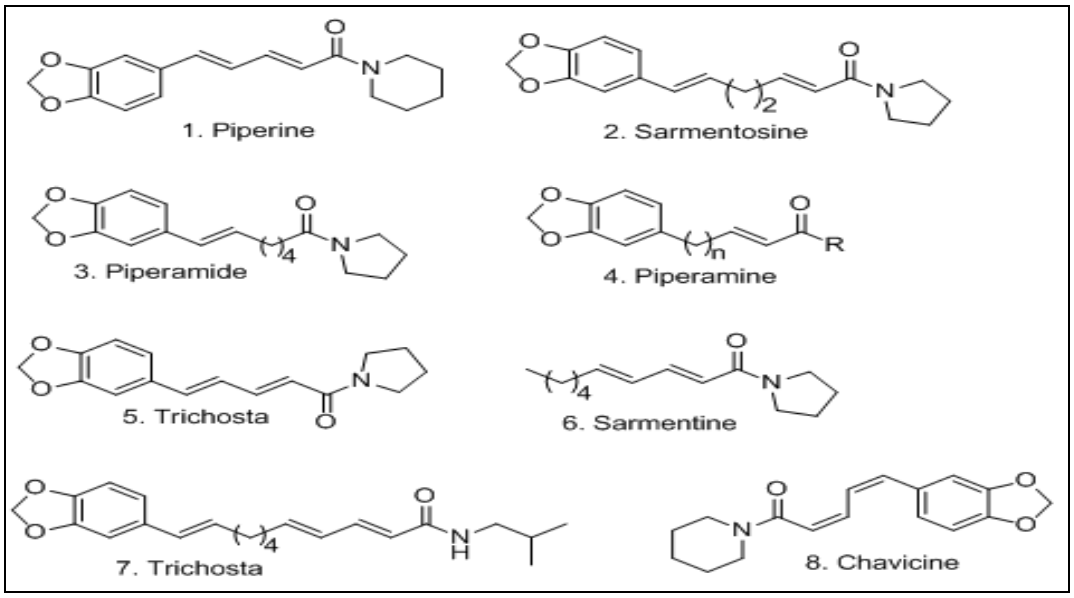

FIG. 2: SOME OF THE IMPORTANT CHEMICAL CONSTITUENT OF *P. NIGRUM*

It has long been used to treat many diseases, such as antihypertensive [9], antioxidant, antiplatelets, antitumor, anticonvulsant, antithyroid, analgesic [6], anti-inflammatory [20, 86], antidiarrheal, anti-spasmodic, antidepressants, immunomodulatory, antibacterial, antifungal, hepatoprotective, *etc.* [1, 7] This has lead scientists to think more about it, as a result there is much research going on regarding its derivative synthesis [78], SAR modification, and testing its biological activities. The traditional and modern uses (Cell, animal and human based study) are summarized in **Table 1**.

Piperine amount varies from 1-2% in long pepper, to 5 - 10% in commercial white and black peppers. It increases the bioavailability of many nutrients and drugs by inhibiting various metabolizing enzymes [1]. Piperine inhibits adipogenesis by antagonizing PPARγ activity in 3T3-L_1 Cells [3]. Like in high fat diet male Wistar rats; 40 mg/kg of piperine significantly reduces body weight, levels of plasma TC (Total Cholesterol), LDL (Low Density Lipo-protein), VLDL (Very Low Density Lipoprotein), and activity of HMG CoA reductase in liver, heart, and aorta, also significantly increase the level of plasma Lecithin Cholesterol Acyl Transferase (LCAT), plasma and tissue lipoprotein lipase (LPL) [5, 10]. Other summarized activities are in **Table 2**.

Thus, piperine is a powerful candidate in regulating obesity induced dyslipidemia, which signifies the great importance of black pepper. Researchers have isolated valuable compounds from black pepper including various lignans derivatives, phenolics, terpenes, chalcones, alkaloid, steroid, flavonoid,

dihydropipericide, N-trans-feruloyltryamine, piperamine and isobutyllocadienamide [11]. They have also isolated, brachyamide B [12], benzamide group [13], (2E, 4E)-N-Eicosadienoyl pereridine [14], guineensine [15], (2E,4E)-N-isobutyldecadienamide [16], piperamide [17], piperettine [19], pipericide [18] and other sarmentine, sarmentosine, piperolein B, trichostachine, *etc*. More than 592 compounds have been isolated and lignans (47), alkaloid/amide (145), terpenes (89), neolignans (70) among them along with 101 novel compounds [11]. Among these 14 compounds, there are biologically active and many SAR modifications going on. The main pungency of *P. nigrum* is due to piperine [94] and chavicine. Chavicine is an alkaloid with diastereomeric geometric isomers of piperine.

TABLE 1: TRADITIONAL USE TO SCIENTIFICALLY PROVEN MODERN USE OF *P. NIGRUM* [1, 3,4-6, 8-9, 15-16, 19-21]

Traditional Use	Modern Use		
	Cell Based Study	**Animal Based Study**	**Human Based Study**
Antiseptic, antispasmodic, aroma, analgesic, anti-inflammatory, anti-toxicant, aphrodisiac, antipyretic, rheumatism, diabetes, muscular ache, diuretic, flavor, spirit, dyspepsia, increase salivary secretion and promote digestion, CNS stimulant, indigestion and flatulence, throat ache, cold, germicidal, blood purifier, antibacterial, religious value, cancer, pungency, kitchen curry, cough, as carminative, insecticide, *etc*	Increase enzymatic activity, increase lipid per-oxidation, antioxidant, bioavailability enhancer, immunomodulatory effect, increase WBC count and inhibit adipogenesis	Antiepileptic, antifertility, bioavailability enhancement, anti-metastatic, stimulate enzymatic activity, inhibit mycobacterium growth, hepatoprotective, increase digestion by promoting bile secretion, synergistic effect in nimesulide, anti-amoebic activity, antifibrotic effect, antibacterial, antioxidant, reduce glutathione, antifungal, *etc*	Anti-asthmatic, anti-oxidant, reduce high fat diet induced oxidative stress, GI stimulant, anti-carcinogenic, lipid metabolism acceleration, anti-inflammatory, cancer, *etc*

TABLE 2: NOTABLE ACTIVITIES OF *PIPER NIGRUM* (WHOLE) AND PIPERINE

Activities/ Model	Dose/ Duration/ Frequency	Result/ Conclusion
		Enhance Bioavailability [60]
Rat		Blood level of vasicine and sparteine increased by piperine and *P. nigrum*, either by promoting fast GI absorption or due to first pass metabolism in liver or both [22]
Rat, Human	5 mg for 14 days	Serum level of *β*-Carotene increased by piperine [23]
	20µmol/L	To overcome vitamin deficiency piperine enhanced β-Carotene uptake [26]
		Curcumin: serum concentration, absorption, bioavailability increased by piperine [24]
Human	2, 4, 5, 6, 7, 8h	Piperine from black pepper *via* oral supplementation, increases plasma levels of coenzyme Q10 [25]
	20 mg; 7 days	Bioavailability of propranolol and theophylline in healthy volunteers was enhanced by piperine [36]
Human, Mouse, Rat	20 mg/kg	Oral bioavailability of phenytoin (anti-seizure medication) was enhanced by piperine [37]
		Affect Enzyme activity and Biotransformation
Mice, Rats and Hamsters.	100 mg/Kg	Piperine showed acute and subacute toxicity, by potentiating CCl_4 induced hepatotoxicity and increased activity of NADPH cytochrome reductase [27]
Rat		Piperine modulate P-glycoprotein ATPase activity (stimulation at low concentration and inhibition at high concentration) [28]
		With direct interaction to enzyme caused impairment of cytochrome $P450_{1A1}$ [29]
Guinea-pig small intestine		piperine lowers the endogenous UDP-glucuronic acid content [30]
		Affect in Digestion
Human	1.5g/ meal	*Via* intragastrical administration of black pepper significantly increase in pepsin and parietal secretion, gastric cell exfoliation and K^+ loss [31]
Albino rat (white)	20-142 mg/kg	Piperine stimulate H_2 receptor and promote gastric acid secretion and was significantly antagonized by cimetidine (H_2 receptor antagonist) [32]
Rat	20 mg %; 8 weeks	Piperine significantly enhanced intestinal lipase activity and the disaccharidases sucrase and maltase in rat; administered along with fed, thus promote digestion [33]
	20 mg/day	Significantly caused shortening of GI food transit time [34]
	12.5 or 25	Feeding piperine along with diet caused an increase in bile flow and decrease in bile

	mg/Kg; 4 weeks	solids, also secretion of uronic acids in bile was enhanced [35]
		Anti-inflammatory, antioxidant, and anti-obesity effects
Rat	20 mg/kg; 10 weeks	Piperine and *P. nigrum* maintained superoxide dismutase, glutathione peroxidase, catalase, glutathione-s-transferase, glutathione levels and reduced high fat diet induced oxidative stress [38]
		Piperine showed anti-inflammatory activity in rats, where acute and chronic experimental models induced by cotton pellet granuloma, rat paw edema and croton oil-induced granuloma pouch; piperine was effective and it also acted partially through stimulation of pituitary adrenal axis [40]
Mouse	1 mg/mL	Piperine inhibit cholesterol uptake and lowered blood lipids [39]
	10 mg/kg	Nimesulide and piperine co-administration showed synergistic effects towards analgesic and anti-inflammatory activity [41]
(Human) Murine dendritic cell	1h, 37°C	Piperine inhibited JNK and ERK pathway, so proved reputed use in arthritis and diabetes [41]
3T3-L_1 Cells		Piperine antagonized PPARγ activity in 3T3-L1 cells, thus inhibits adipogenesis [3]
		Anti-carcinogenic and Anti-mutagenic effects
Mouse	0.98 mg	Significantly piperine inhibited lungs metastasis-induced B16F10 melanoma cells in mice [43]
		P. nigrum, oral administration increased life span of mice with tumor (*Ehrlich ascites*) [44]
	50 mg/kg	Lipid peroxidation, nucleic acid content, protein carbonyl and carcinogenesis are significantly prevented due to preventing protein damage and suppressing cell proliferation by piperine [45]
Rat		Chemical carcinogenesis was inhibited by *P. nigrum* through modulating glutathione-S-transferase, Cytochrome P-450, malondialdehyde levels, and acid soluble sulfhydryl content [46]
		Role in fertility and Hormonal effect
Rat	5-10 mg/kg	Piperine cause marked increase in serum gonadotropin, significant decrease in weight of testes and decrease in intra-testicular testosterone level without change in normal serum testosterone titres [47]
		Infusion of piperine in rat, induced catecholamine secretion from the adrenal medulla [48]

A large variety of aromatic and volatile compounds are present in *P. nigrum* and it possesses diverse potential for cosmetic, perfumery, medicine, and kitchen spices. Some of the categorized aromatic and volatile principles found in it are summarized in **Table 3**.

TABLE 3: AROMATIC AND VOLATILE COMPOUNDS PRESENT IN *P. NIGRUM* [21, 49]

Monoterpenes	Sesquiterpenes	Others
Sabinene	Caryophyllene oxide	Cinnamic acid
Limonene	α-Cis-Bergamotene	Benzaldehyde
Camphene	α-Trans-	Eugenol
Myrcene	Bergamotene	Methyleugenol
Cis-Ocimene	α-Copaene	Myristicin
Terpinolene	α-Cubebene	m-Methyl
1,8-Cineole	α-Selinenes	acetophenone
α-Thujene	β-Bisabolene	n-Butyrophenone
α-Pinene	β-Caryophyllene	Piperonic acid
α-Phellandrene	β-Cubebene	Piperonal
α-Terpinolene	β-Elmenes	Phenyl acetic acid
β-Pinene	γ-Cadinene	P-Methyl
β-Phellandrene	δ- Cadinene	acetophenone
γ-Terpinene	ar-Curcumene	Safrole
δ^3-Carene		Trans-Anethole

The species possesses flavor, color and aroma also provides diverse therapeutic potency. Many writings of the Ayurveda describe the diversified use of *P. nigrum.* Day-to-day, new updates in its research for specific pharmacological action established by experimental and clinical studies signifies the traditional ethnomedicinal use of *P. nigrum*. Many active constituents are already being isolated from it and among them, some show significant pharmacological potency.

Some of the notable pharmacological activity showed by *P. nigrum* and its isolated constituents that attracts our todays research are antioxidant, antibacterial [79], antiviral, antifungal, antimicrobial, anti-adipogenesis, insecticidal, larvicidal, pesticide, anti-diarrheal, analgesic and antipyretic, anti-apoptotic, antidepressant, antimutagenic and anticancer, immunomodulatory, antispasmodic, anti-thyroid, cold extremities, gastric ailments, hepatoprotective, increase pancreatic enzymes, inhibit cytochrome, *etc*. which are summarized in **Table 4** along with references of individual activities. Recent studies have shown that it is helpful in enhancing the absorption of Vitamins,

selenium, β-carotene, and promoting body thermogenic activity naturally [56]. Some physiochemical studies on pepper starch with comparison to other starch will give new application way in near future [81]. Recent research is more focused to the dynamic use of piperine by formulating different dosage forms [82, 88, 92, 93].

Various patent are registered claiming novel use of piperine [40, 78, 89]. Now it is not only limited to the activity but also many attempts are made to know the mechanism, biological pathway for activity shown by piperine [90, 91]. An individual description below shows some of the elaborated literature review of the above potency.

Evidence Based Pharmacological Activities of *P. nigrum* and Piperine: Using internet search engine, accessing to different journals, this attempt has been made to collect some update research on *P. nigrum* or its active constituents (Piperine). Below **Table 4** shows some of the summarized pharmacological activities of *P. nigrum* and piperine.

TABLE 4: PHARMACOLOGICAL ACTIVITIES OF *P. NIGRUM*

S. no.	Activities	S. no.	Activities
1	Anti-diarrheal [8]	15	Effects in metabolism [15, 23, 30]
2	Antimicrobial [50,84,85]	16	Effect on enzyme [16, 25, 28, 29, 33, 41]
3	Antioxidant [9, 38, 93]	17	Effects in neurodegeneration and cognitive impairment [17]
4	Anticancer [19] and tumor reduction activity [43, 44, 45]	18	Effect in Bioavailability [22, 24, 26, 60]
5	Antihypertensive [9]	19	Toxicity activity [27]
6	Anti-asthmatic	20	Effects in stomach [31, 32]
7	Anti-inflammatory [20, 40, 86]	21	Decrease food transit time [34]
8	Anti-obesity [5, 39], Antidiabetic [87]	22	Effect in bile secretion [35]
9	Hepatoprotective activity [46]	23	Effect in pharmacokinetic of drugs [36, 37]
10	Digestive activity [31, 32, 34, 35, 33]	24	Synergistic effect with drugs [42]
11	Antidepressant [16]	25	Inhibition of lungs metastatis [43]
12	Immunomodulatory activity	26	Fertility effect [47]
13	Analgesic and Antipyretic activity [6]	27	Hormonal activity [48]
14	Anti-adipogenesis activity [3]	28	Anthelmintic activity [75]

Taxonomical Classification of *Piper nigrum:*

Kingdom : Plantae
Subkingdom : Tracheobionta
Superdivision : Spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Sub class : Magnoliidae
Order : Piperales
Family : Piperaceae
Genus : *Piper*
Species : *nigrum* L.

Antioxidant Activity: Free radicals are responsible for causing many diseases. Different kinds of free radicals can attack the cell membrane, and cause or alter membrane permeability, membrane damage, oxidation of lipids, loss of different enzymatic activities, and ultimately disrupt proper cell function and body physiology, which may cause cancer. There are many antioxidants in our body to scavenge the free radical generated normally during metabolism. However, it can be insufficient sometimes. When there is imbalance between the free radical generation and antioxidant activity, oxidative stress is induced; which is harmful to our body, causing many side effects from simple health problems to cancer. Antioxidant activity of our body system includes enzymes like catalase, ascorbate, peroxidase, and superoxide dismutase, which are responsible for scavenging both free radicals and related oxygen species. Plants are a potent source of antioxidant activity from ethnomedicinal practices to today's finding.

Many scientific findings prove its great antioxidant potency [38, 56]. Piperine and *P. nigrum* maintain superoxide dismutase, glutathione peroxidase, catalase, glutathione-s-transferase, glutathione levels and reduce high fat diet induced oxidative stress [38]. Many screenings, using different solvent system for extraction of *P. nigrum* constituents, prove this potency [77]. The ethanolic extract of *P. nigrum* shows high antioxidant potency with 74.61 ± 0.02% with IC_{50} value 14.15 ± 0.02 µg/mg [56].

The methanolic extract of *P. nigrum* fruits showing memory enhancing and antioxidant potency at a dose of 50 and 100 mg/kg, orally for 21 days in amloid-*β* (1-42) were investigated in rat model of alzheimer's disease [1, 38]. Research in Piper species *viz. P. nigrum, P. guineense* and *P. umbellatum* shows effects such as protecting cardiac, hepatic, and renal antioxidant status of atherogenic diet fed hamster at a dose of 1g/kg and 0.25g/kg for 12 weeks. The significant inhibition of atherogenic diet induced increased lipid profile and alteration in antioxidant enzyme activities; showed a great antioxidant protective role of the piper extract against atherogenic diet generated oxidative stress in cardiac, hepatic, and renal tissues [61]. Thus, it will have important role in scavenging free radicals and delay aging process. As reported, *P. nigrum* has antioxidant potency that may be due to presence of flavonoids and phenolic contents [1, 77].

Antimicrobial Activity: An antimicrobial is an agent that kills micro-organism or inhibits their further growth. These antimicrobial agents can be grouped into different categories according to their primary activity, like antibacterial, antifungal, antiviral, anti-parasitic, pesticide, *etc*. Many plants have been used as an antimicrobial agent throughout time and will be in future. Although any modern synthetic antimicrobial agents are developed rapidly, the resistance towards them is also growing rapidly. Usually the resistant against plant source seems less when compared to modern chemical drugs, this may be due to presence of a wide variety of different chemical constituent within a single plant.

Many literature reviews have shown the antimicrobial potency of black pepper [80]. Extract of black pepper using solvent *viz*. carbon tetrachloride, benzene, ethyl acetate, acetone, methanol, ethanol, and distilled water were tested against gram-positive and gram-negative bacteria *viz. Staphylococcus albus, S. typhi, E. coli, B. megaterium, P. aeruginosa* and one fungus, *Pseudomonas aeruginosa* [77]. Against different bacteria, the strongest antibacterial and antifungal activity was shown at the concentration of 40µg/disc [50]. Using *P. nigrum* leaf and stem extract, the silver nanoparticle was synthesized, and the antibacterial activity was examined against the agricultural plant pathogen which showed excellent activity, thus the author concluded its beneficial application in the field of agricultural nanotechnology [62]. All 20 strains of *K. pneumoniae* were isolated from the urine culture of a hospitalized patient suffering from urinary tract infection (UTI) and alcoholic extract of *P. nigrum* was tested against it, which showed good activity against antibiotic resistant *Klebsiella pneumonia* with MIC and MBC value at 0.62 mg/ml [51].

The evaluation of essential oil from *P. nigrum* for repellent, developmental inhibitory, and insecticidal activity against wheat grain pest *Tribolium castaneum* showed that the adult of *T. castaneum* at 0.2% concentration (v/v) repelled it significantly. The LD_{50} for larva and adult was 14.022 µL and 15.262 µL respectively. The effective concentration (EC_{50}) to decrease the larva transferred to the pupae to 50% was 6.919 µL [54]. A protozoal infection, visceral leishmaniasis (VL) is a life-threatening disease in rural areas and the poor population in the tropical and sub-tropical countries. The *P. nigrum* hexane (PNH) and *P. nigrum* ethanolic extract (PNE) of seeds of black pepper showed profound leishmanicidial activity against L. *donovani* promastigoates and amastigoates *via* apoptosis [53].

The antibacterial activity of *P. nigrum* carried out against *B. subtilis, S. aureus, P. aeruginosa, E. coli, A. niger, A. alternate, A. flavus and F. oxysporum* showed zone of inhibition from 8-18 mm range. Maximum for gram positive bacteria *S. aureus* (18 mm) and minimum against gram negative bacteria *E. coli* (8 mm). Similarly, piperine maximum anti-fungal activity against *Fusarium oxysporum* (14 mm) and least against *A. niger* (38 mm) [59]. The chloroform extract of black pepper showed significant damage to bacterial cell membrane of *E. coli*, and *S. aureus* followed by disruption of respiration [83]. All these significant antimicrobial effects in wide variety of micro-organism signifies *P. nigrum* as a powerful natural antimicrobial agent.

Antidiarrhoeal Effect: Along with above described antimicrobial activity of black pepper, against some bacteria[77] which are also responsible for causing diarrhea. Other research signifies its great potency in controlling diarrhea. As we know, diarrhea is a leading cause of morbidity and

mortality globally, especially among the children in developing countries.

Aqueous extract of black pepper at a dose of 75, 150, 300 mg/kg, produces a significant dose-dependent antimotility, anti-secretory and anti-diarrheal effects. The author concluded that this effect is due to the presence of carbohydrates and alkaloids in black pepper [8].

Analgesic, Antipyretic and Anti-Inflammatory Activity: *In-vivo* analgesic activity of piperine was evaluated in mice. The analgesic activity was tested by using acetic acid-induced writhing, tail flick assay. After intraperitoneal (i.p.) injection of piperine (30, 50 and 70 mg/kg), the acetic acid-induced writhing in mice was observed and found to be significantly inhibited (P<0.01), like the effect of indomethacin- an NSAID drug (20 mg/kg, i.p.). In the tail flick assay, morphine (5 mg/kg, i.p.) and piperine (30 and 50 mg/kg, i.p.) showed a significant increase (P<0.01) in the reaction time of mice. Animals with naloxone pre-treatment (5 mg/kg i.p.), reversed the analgesic effects of both morphine and piperine. All these findings reveal that piperine exhibits analgesic effects possibly mediated *via* opioid pathway [63].

Analgesic activity of piperine was tested in mice (20 and 30 mg/kg, i.p.); acetic acid and hot plate reaction test was used. Indomethacin (10 mg/kg) was taken as reference standard. Piperine showed significant (p<0.5) dose dependent delayed response towards pain. The antipyretic activity of piperine was observed by using yeast-induced pyrexia in mice model. The rectal temperature was measured in piperine (20 and 30 mg/kg) treated mice as compared to the control group. Where the significant (p<0.5) increase in temperature in the control group mice was observed [6]. The experiment revealed that anti-inflammatory, analgesic, and anti-arthritic activity of piperine in arthritis model of rat. For measuring *in-vitro* anti-inflammatory activity, the interleukin 1β stimulated synoviocytes taken from rheumatoid arthritis was used. While the anti-arthritic including analgesic potency was carried out on carrageen, an induced acute paw model or arthritis and pain in rat. The cyclo-oxygenase 2, interleukin 6, prostaglandin E2 and matrix metallo-protease levels were tested by RT-PCR and ELISA analysis method. At concentration of 10-100µg/mL, piperine treated group were found to reduce synthesis of PGE2 in a dose dependent manner. Even at 10 µg/mL it significantly inhibits the synthesis of PGE2. The expression of metallo-proteinase 13 and interleukin 6 were also inhibited [65]. Which concludes the potency of piperine for the titled topic.

Anticonvulsant Effects: The mice model for anticonvulsant activity of piperine was evaluated by inducing seizure with pentylenetetrazol (PTZ)- and picrotoxin (PIC) in mice. On administering piperine (30, 50 and 70 mg/kg, i.p.) and reference standard drugs, valproic acid (200 mg/kg, i.p.), diazepam (1 mg/kg, i.p.) and carbamazepine (30 mg/kg, i.p.) which showed significantly (P<0.01) delayed onset of PTZ-and PIC-induced seizures in mice. Which indicate that piperine exhibits anticonvulsant effects possibly mediated *via* GABA-ergic pathways [63].

Another experiment on anticonvulsant activity of piperine in pentylenetetrazol (PTC) and maximal electroshock (MES) model of convulsion in mice showed a delay in onset of generalized chronic seizure and myoclonic jerks with administering piperine (40- 80 mg/kg) and a significant reduction of PTZ-induced Fos immune reactivity in dentata gyrus and MES-induced tonic hind limb extension after piperine administration. The capsazepine, a selective TRPV1 antagonist blocked the anti-seizure effect of piperine [64]. These findings reveal the potent anti-convulsant activity of piperine.

Antitussive and Bronchodilator: Many traditional practices prove it as well. *P. nigrum* is widely used in many herbal cough syrups due to its potent antitussive and bronchodilator properties [60]. Many old people and herbal practitioners believed that the addition of little amounts of powered peppercorn in a green tea significantly reduces asthma [4]. The oral administration of piperine in different amount to mice reduced and suppressed the hyper responsiveness, infiltration of eosinophils and inflammation possibly due to suppression of production of histamine, immunoglobulin E, interleukin 4 and interleukin 5 [66].

Anti-obesity Activity: Obesity is becoming a global problem, since it is a socially stigmatized health problem. The modern treatments are only

effective when they are used, and the problem progresses again after stopping drug use. On the other hand, the drugs have more side effects. So, experiments are now focusing on herbal medicine and other non-pharmacological way of management of obesity like exercise, yoga, meditation, diet control *etc*.

There are so many plants that have anti-obesity potency among them, *P. nigrum* is one. In an anti-adipogenesis study of *P. nigrum* extract and piperine in 3T3-L1 preadipocytes both the black pepper extract and piperine strongly inhibited the adipocyte differentiation of 3T3-L1 cells, without affecting cytotoxicity. The mRNA expression of masteradipogenic transcription factor, SREBP-1c, C/EBPβ and PPARγ were significantly decreased. Piperine disrupts the rosiglitazone- dependent interaction between PPARγ and cofactor CBP in GST pull down assay.

Furthermore, in genome-wide analysis using microarray supports the potent role of piperine in gene regulation associated with lipid metabolism [3]. In another experiment, supplementing piperine with high fat diet (40 mg/kg) significantly reduced not only body weight, total cholesterol, triglyceride, LDL, VLDL and fat mass but also increased the level of HDL, with no change in food intake [5]. These results suggest black pepper possesses potential lipid lowering and fat reducing effects, without any change in the food appetite.

In another study, black pepper was given to a high-fat-fed rat in two different doses of 250 mg/kg and 500 mg/kg and piperine at 20 mg/kg was administered for 10 weeks and the plasma and tissue lipid profile showed significant reduction in total cholesterol, phospholipids, free fatty acids, and triglycerides in both groups. Thus, these all results suggest that dietary intake of black pepper or piperine reduces the risk of arthrosclerosis *via* hypolipidemic and antiatherogenic effects [58].

Antimutagenic, Antitumor and Anticancer Activity: Cancer is becoming global challenge in today's health system. Although enormous efforts are done and going on to find new technology, drugs, research, surgery, it is still insufficient. So, we need to search such systems where negligible side effect with high therapeutic outcomes. Chemo-therapy is very painful to a patient and has other serious adverse effects. Many herbal medicines are used in different systems of medicine, such as Ayurveda, Chinese, Homeopathy, and so on. Plant sources are believed having no/negligible side effects. We should use herbal medicine in our daily life along with food to avoid cancer and tumors in our lives. To signify this potency, black pepper has been used as an anticancer and antitumor agent. *P. nigrum* has been reported in many literatures as having the potency to inhibit tumor formation in different experimental models [1].

Ethanolic extract of peppercorn and piperine showed effective immunomodulatory and antitumor activity [1]. As we know, angiogenesis plays a key role in tumor progression and cancer. Research findings show that piperine inhibits proliferation and G1/S transition of human umbilical vein endothelial cells (HUVECs) without causing cell death, and also inhibits migration of HUVEC and *in-vitro* tubule formation and angiogenesis induced by collagen and breast cancer cell in embryo of chick.

Moreover, the phosphorylation is an essential controller in angiogenesis process and function of endothelial cells. Interestingly, piperine also inhibits phosphorylation of Thr 308 residues of Akt of protein kinas B and Ser 473 too. Thus, piperine can be a good agent for controlling angiogenesis in cancer treatment [67]. Prostate cancer is a big problem for men, causing thousands of deaths a year. Research has shown that piperine has good anticancer activity against prostatic cancer cells of both androgens dependent and independent. A dose dependent inhibition of the proliferation of 22RV1, DU-145, PC-3 and LNCaP prostate cancer cells by piperine was investigated [68]. Piperine from black pepper modulate lipid peroxidation and activation of antioxidative protection enzyme, thus reduced lung cancer [69, 70].

Anticancer and cancer prevention potency of piperine free *P. nigrum extract* (PFPE) against the N-nitrosomethyllurea (NMU)-induced mammary tumorigenesis in rat and on breast cancer cells was carried out and the result showed potent inhibition in growth of luminal like breast cancer cells *via* induction of apoptosis. Moreover, PFPE showed a higher selectivity against breast cancer cells than

lungs cancer, neuroblastoma cells and colorectal cancer. In an acute toxicity test, a dose of 5g/kg single dose for 14 days observation period showed no mortality and morbidity. The mechanism of action and cytotoxicity effect in breast cancer cells was measured by Western blot analysis and MTT assay respectively [57]. Piperine inhibited growth of 4T1 cells at a dose of 35-280 µmole/L in dose and time dependent manner with IC_{50} were 105 ± 1.08 and 78.52 ± 1.06 µmole/L respectively at 48 and 72h. At 70-280 µmole/L dose dependently induced apoptosis of 4T1 cells *via* activation of caspase 3. Piperine injection (5 mg/kg) significantly inhibited lung metastasis and at injection dose (2.5 and 5mg/kg) cause marked suppression of 4T1 tumor growth dose-dependently [52].

Anxiolytic and Antidepressant Activity: In this globalized world, people are more stressed. Suicide and mental sub-activity is a big problem in today's society. Many herbs are used as a memory enhancer. Among which, black pepper has been used for a long time in herbal and ethnomedicinal practice [22, 76]. Today's more scientific experimental model findings prove it is useful. Anxiolytic and antidepressant activity of the methanolic extract of *P. nigrum* fruits in beta-amyloid (1-42) treated rat model of Alzheimer's disease showed increase in immobility and decrease in swimming time within forced swimming test. Whereas decreases in % of time spent, exploratory activity and number of entries in open arm within elevated plus-maze test.

This showed the methanolic extract significantly exhibited antidepressant and anxiolytic effects by attenuation of oxidative stress [55]. Another study was done in corticosteroid induced depression model of mice. After 3-week corticosterone injection mice showed depression like behavior observed by tail suspension test and immobility time in forced swim test. These depression behaviors are significantly diminished after piperine administration [71]. Those finding proves the potent anxiolytic and antidepressant activity of black pepper.

Digestive and Hepatoprotective Activity: Many experimental findings show the hepatoprotective effect of *P. nigrum* in animal and human model [4]. The methanolic extract from black pepper (MEPN) fruits (100 and 200 mg/kg, p.o. for 15 days) and piperine (50 mg/kg, p.o. for 15 days) were tested against ethanol-CCl_4 induced hepatotoxicity Wistar rats, which reveals the significant activity of black pepper in decreasing the hepatic biomarker level like TG, AST, ALT, ALP and bilirubin, which were increased on ethanol-CCl_4 administration. The significantly decreased level of SOD, GSH and CAT after ethanol-CCl_4 administration were restored with MEPN and piperine. These results were like the reference standard Liv 52 (1ml/kg, p.o., 15 days) [72].

Another study where liver toxicity in mice was induced with D-galactosamine and exposed to dose dependent piperine, which inhibited increase in serum GOT and GPT levels and suggested that this effect dependend on hepatocytes reduced sensitivity towards tumor necrosis factor-α [73]. Those study reveals that the *P. nigrum* possesses potent hepatoprotective properties which can be used as therapeutic potential in liver disorder.

The pungent properties of *P. nigrum* specially the piperine increases production of the saliva, activate salivary amylase, and promote gastric secretion, more over decrease GI transit time [74]. The use of black pepper as spicy is more. Black pepper 1.5g/meal administration in healthy human volunteer *via* intragastrical administration significantly increases pepsin and parietal secretion, gastric cell exfoliation and potassium loss [31]. In rat model administration of piperine 20 mg% for 8 weeks along with fed significantly enhanced intestinal lipase activity and disaccharidases the maltase and sucrose, thus promote digestion [33].

Other Pharmacological Activities and Use: *P. nigrum* (Black pepper) exhibits many pharmacological actions like antiplatelets, anti-hypertensive, antispasmodic, antiprotozoal, bioavailability enhancer [60], memory enhancer, antimutagenic, insecticidal, immunomodulator, antithyroid, anti-asthmatic, anxiolytic activities *etc.* [1, 47, 52, 55].

CONCLUSION: Black pepper is a very rich source of a wide variety of chemical constituents, most of which are biologically active. The long practice of using pepper in different traditional systems of medicine made its scope from the

kitchen, to drugs, to cosmetics. Modern experimental research on the different biological activities reveals the significance of its use in traditional systems of medicine. Many scientific elaborations about its volatile constituents, monoterpenes, sesquiterpenes, and specially piperine have increased the scope in the field of further activity testing its medicinal and other uses.

Moreover, the synthetic modifications to make a more potent drug candidate with minimum toxicity and great significance. New researches are going on, using different formulation, method of use, linked with other delivery technology where the pepper is the main constituent. The pepper's use in treating cancer, obesity, hypertension, diabetes, diarrhea, and its bioavailability signifies its attraction in the future. Furthermore, specific research studies are needed to signify the black pepper is miraculously really the King of species.

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