A REVIEW ON BIOACTIVE CHEMICAL COMPOUNDS, TRADITIONAL MEDICINAL USES AND PHARMACOLOGICAL ACTIVITIES OF *PIPER NIGRUM* L. SEEDS: DEMAND OF THE TIME:

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Abstract:
Medicinal plants are very popular in different traditional systems of medicines due to their diverse Pharmacological potentials and lesser side effects in biological systems. Moreover, only a very limited number of plants have been studied and scrutinized in detail; thereby prompting WHO to recommend that this area be comprehensively investigated. Black pepper fruit (*Piper nigrum* L.) is one of the most famous pungency and flavored spices in the world, it is known as the king of spices. It contains a pungent alkaloid ‘‘piperine’’ which is known to possess many pharmacological actions. It has numerous bioactive effects on the human body. One of these benefits is its noticeable antibacterial activity. Recent scientific researchers have established the presence of many active compounds in this spice that are known to possess specific pharmacological properties. The therapeutic efficacy of this individual spice for specific pharmacological actions has also been established by experimental and clinical studies. Piperine which is an alkaloid that has diverse pharmacological activities like antioxidant, anti- obesity, antitumor, antipyretic, anticonvulsant, anti-tussive, antimicrobial, hepatoprotective, anti-asthmatic, antihypertensive, anti-inflammatory, antidiabetic, antidiarrheal, bioavailability enhancer, immunomodulator, anticancer, anticonvulsant diuretic, aphrodisiac, blood purifier and antiplatelet activities, *etc*. The current review article is aimed to provide an updated literature review on recent advancement of pharmacognosy, chemistry and pharmacological activities of *Piper nigrum* L.

KEYWORDS: *Piper nigrum* L., Traditional medicinal uses, Bioactive Compounds, Pharmacological Activities

Introduction:

Plants have been a major source of medicine for mankind. The use of plants and plant products as medicines could be traced back as the beginning of human civilization. The earliest mention of medicinal use of plants is found in “Rigveda”,which is said to have been written between 4500-1600 B.C. and supposed to be the oldest repository of human knowledge(Gupta et al 2010) and (Kumar M. 2015). According to available information, a total of at least 35,000 plants species are widely used for medicinal purposes. The demand for traditional medicinal herbs is increasing very rapidly, mainly because of the undesirable side-effects of some synthetic chemical drugs. Nowadays, the interest in natural products as antimicrobial agents has greatly increased due to the gradual collapse of antibiotics due to the multi-drug-resistant pathogens (Abdullah EM, Koko WS 2017).

Spices are rich in bioactive chemical compounds and they have been used by several cultures for many centuries as food seasoning, preservatives, insecticidal, colorants, and natural flavoring agents. Elizabeth TJ, Gassara F, Kouassi AP, et al.,(2015), Gupta N, Parashar P, Mittal M, et al. (2014). Many spices are used to increase shelf-life of food, prevent food spoilage and to avoid from food-borne diseases, though some spices are used in food production industry and also many spices are used to inhibit infectious diseases and eradicate pathogens, particularly in traditional system of medicine (Liu Q, Meng X, Li Y, et al., 2017) The

antibacterial efficacy of some spices and seasonings have been proved scientifically, as example of these spices; black seed (*Nigella sativa*), Abdullah EM 2017, garlic bulb (*Allium sativum*), Rahman MS, Al-Sheibani HI, Al-R, iziqi MH, et al.,2006 onion (*Allium cepa*), Kim JH,1997 ,Thyme (*Thymus vulgaris*) and clove (*Syzygium aromaticum*), Nzeako BC, Al-Kharousi ZSN, Al-Mahrooqui Z.,2006 cinnamon bark (*Cinnamomum verum*), Julianti E, Rajah KK, Fidrianny I.,2017, oregano (*Origanum vulgare*), Saeed S, Tariq P, 2009, cumin (*Cuminum cyminum*) Allahghadri T, Rasooli I, Owlia P, et al, 2010 and many more.

The current review aimed to highlight the medicinal importance of black pepper seeds / fruits and also its efficacy as antibacterial agent. *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. It is one of the world's 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, and Milagu in Tamil, and Black Pepper, Peppercorn, Green pepper, White pepper, Madagascar pepper in English (Damanhouri ZA and Ahmad A, Meghwal M and Goswami TK, 2014). It is widely accepted and most used in different traditional systems of medicine, like the Unani and Ayurvedic systems (Ahmad N, Fazal H, Abbasi BH, Farooq S, Ali M and Khan MA, 2012).

Taxonomic classification

Kingdom: Plantae
Sub-kingdom: Tracheobionta
Super-division: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Magnoliidae
Order: Piperales
Family: Piperaceae
Genus: *Piper*
Species: *nigrum*

P. nigum is a woody climbing vine growing to 9 m (30 ft) or more in length. The grayish stem may reach 1.2 cm (0.5 in) diameter. Numerous rootlets grow from swollen stem nodes. Leaves dark green above and pale green beneath, glossy, ovate and acutely tipped, and range in size from 13–25cm (5–10 in) in length. Elongated, slender spikes or catkins (1.6–2cm [4–5 in] in length) bear minute, white flowers. The flower spikes, each producing from 50–60 single-seeded dark red berries, approximately 5millimeters (0.20 in) in diameter, always appear on stems opposite the leaves (Nelson SC, Eger KT, 2011). Different parts of the plant are used for medicinal purposes; however, the part commonly used as the spice black pepper is the cooked and dried unripe berry, (Charles DJ, 2013) that is why I have focused only on the use of this plant part.

Fig: Black Pepper Seeds

Distribution:

A branching, climbing perennial shrub, mostly found cultivated in the hot and moist parts of India, Ceylon, and other tropical countries. Black pepper is one of the most cultivated crops in India and has probably originated in the hills of Southern-Western India Anonymous, 1969. It is mostly found in Southern India and is cultivated in Tamil Nadu and Kerala and also found in Singapore, Acheen and Lampong districts of Sumatra, Sri Lanka, France, Indonesia, Thailand, South America, and West Indies, Anonymous, 1987. It is indigenous to Malabar Travancore coasts, i.e. western coast of India, (Nadkarni KM, 1989). Black pepper has been found throughout India in evergreen forests up to 1500 m (Warrier PK, Nambiar VP, Ramankutty C., 1997).

Bioactive chemical compounds of the black pepper:

Almost all spices have aromatic features, regular grindings of spices lead to loss of important aroma compounds and accordingly resulted to considerable loss of aroma and flavor components and deterioration of quality (Murthy CT, Bhattacharya S, 2008). The dried black pepper fruit is rich in bioactive phytochemical compounds. Piperine (Figure 2) is one of the most abundant chemical alkaloids in the black pepper(Kunnumakkara AB, Koca C, Dey S, et al,2009).Other similar alkaloids are also isolated from black pepper such as piperanine, piperettine, piperylin A, piperolein B, and pipericine. However, the pungency of these piperine's analogs are less than the Piperine (Gorgani L, Mohammadi M, Najafpour GD, et al, 2017). Black pepper was also found to have a good quantity of polyphenols. The interesting findings are that, black pepper contains more polyphenols compared with white pepper. Moreover, it is believed that, after eating Black pepper, it hydrolyzed in the gut and liberating these bound polyphenols(Agbor GA,Vinson JA, Oben JE, et al,2006) Even some studies stated that the Black pepper contains aromatic compounds, flavonoids, alkaloids, amides and lignans.(Agbor GA,Vinson JA, Oben JE, et al,2006). The volatile oils of the Black pepper fruits were analyzed using column chromatography, high resolution gas chromatography and gas chromatography mass spectrometry (GC-MS); up to 46 compounds were identified including δ-cadinol, δ-guaiene, (Z) (E)- farnesol, (E)-β-ocimene and guaiol (Pino J, Rodriguez-Feo G, Borges P, et al, 1990). In another study, five phenolic amides were isolated from the black pepper, which revealed high antioxidant activity more effective than some naturally occurring antioxidants (Nakatani N, Intend R, Ohta H, et al, 1986). All these investigations revealed the wealth of the black pepper in bioactive phytochemical components of promising medicinal importance.

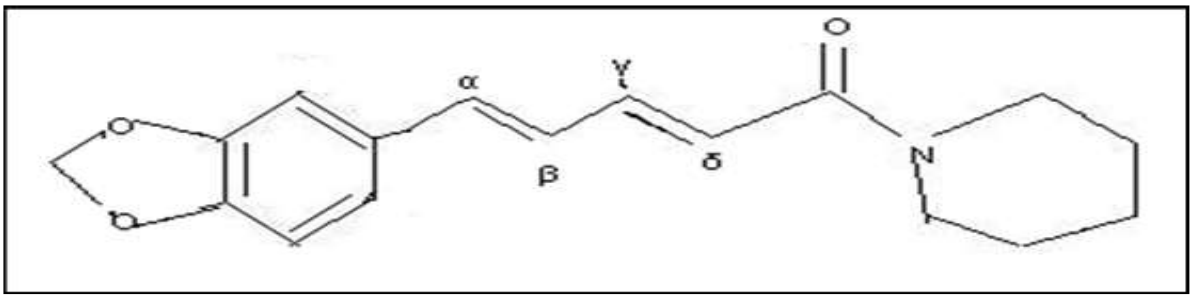

Figure 2 Piperine, the major compound in the Black pepper fruit

Traditional Medicinal uses:

In the classical literature, many Unani scholars have mentioned various medicinal uses of black pepper. It has been described for its efficacy in cholera, dyspepsia, flatulence, diarrhea, and other gastrointestinal ailments. It is also a useful ingredient in tooth powders. In "Ilaj-ul-Ghurba" a pill is recommended for syphilis, which is prepared by taking black pepper (*P. nigrum*), *Calotropis gigantea*, and jaggery. Externally, it is applied to boils. It is also used in case of sore throat, alopecia, skin disorders, and piles etc. Finely powdered black pepper and seasame oil well mixed and heated, when applied over the paralytic area, is proved to be very effective. A preparation made with black pepper and leaves of *Cassia occidentalis* is even good for night blindness. It is also used in the treatment of gonorrhea. The drug is used as an antidote for scorpion sting (Nadkarni KM, 1989). The plant *Cissampelos pareira*, in combination with black pepper, has been claimed to be useful in birth control when given immediately after delivery. In Cambodia, it is also used as cure for dysentery (Kritikar KR, Basu BD, 1987). In reference with Dioscorides, it is mentioned in Al-Jama-al-Mufradatal- Advia-wo-al-Aghzia, that it is beneficial for the treatment of cough and chest pain when given in the form of sharbat (Syrup) or lauq (Paste). Along with honey, it is good for diphtheria. The combination of black pepper, onion, and salt, when applied on the bald area, is effective for curing alopecia. When used along with vinegar, it is also good for teethache (Al Baitar Z. Al-Jama-al Mufridat-al Advia-wo-al Aqhzia, 1999).

PHARMACOLOGICAL ACTIVITIES:

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 (Bukhari IA, Pivac N, Alhumayyd MS, Mahesar AL and Gilani AH, 2013).

Antimicrobial activity of black pepper:

Khan and Siddiqui in 2007 evaluated the antibacterial potential of aqueous decoction of *Piper nigrum* L. (black pepper), *Laurus nobilis* L. (bay leaf), *Pimpinella anisum* L. (aniseed), and *Coriandum sativum* L. (coriander) against different bacterial isolates from oral cavity of two hundred individual volunteers. Black pepper (aqueous decoction) showed strongest antibacterial activity comparable to aqueous decoction of *Laurus nobilis* and *Pimpinella anisum* at the concentration of 10µL/disc (Khan M, Siddiqui M, 2007). In a recent study, the silver nano-particles from leaf and stem extract of *Piper nigrum* were synthesized and then antibacterial activity of the synthesized silver nanoparticles of *Piper nigrum* was evaluated against agricultural plant pathogens. These silver nano-particles showed the excellent antibacterial activity against plant pathogens. It was concluded that the antibacterial activity of silver nano-particles is a beneficial application in crop improvement and protection in agricultural nanotechnology (Kumar KP, Gnanajobitha G, Vanaja M, Kumar SR, Malarkodi C, Pandian K, et al., 2014)

Antidiarrhoeal Effect:

Along with antimicrobial activity of black pepper, against some bacteria (Sapam R, Kalita PP, Sarma MP, Talukdar N and Das H,2018) which are also responsible for causing diarrhea. Research also 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 antidiarrheal effects. It was concluded that this effect is due to the presence of carbohydrates and alkaloids in black pepper (Shamkuwar PB, Shahi SR and Jadhav ST, 2012).

Anti-cancer activity of black pepper:

Piper nigrum had been reported to inhibit tumors formation in different experimental models. Many studies revealed the antitumor activity of *P. nigrum* or Piperine by the oral administration. The alcoholic extract of peppercorn and piperine exhibited effective antitumor activities. Piperine is also reported to reduce the lung cancer by altering lipid peroxidation and by antioxidative protection by enzymes activation (Ahmad N, Fazal H, Abbasi BH, Farooq S, Ali M, et al., 2012). Piperine was reported to inhibit G1/S transition and the proliferation of human umbilical vein endothelial cells (HUVECs), migration of HUVECs and *in vitro* formation of tubule and angiogenesis induced by collagen and breast cancer cell in chick embryos. Piperine also inhibits the phosphorylation of Thr 308 residues of Akt of protein kinase B as well as Ser 473. Since phosphorylation of these is an essential controller of angiogenesis and function of endothelial cells. Therefore, Piperine may be used as an inhibitor of the angiogenesis for the treatment of cancer as angiogenesis plays a key role in the progression of tumor (Doucette CD, Hilchie AL, Liwski R, Hoskin DW, 2013). Docetaxel (a cytotoxic chemotherapeutic agent) is a FDA approved drug for the treatment for castration-resistant prostate cancer. The metabolism of docetaxel occurs in the liver by hepaticCYP3A4, and piperine is reported to inhibit the hepatic CYP3A4 enzymatic activity. Therefore, the administration of docetaxel in combination with piperine was investigated for both *in vitro* and *in vivo* pharmacokinetic activity of docetaxel. It was also reported that nutritional use of piperine increased the efficacy of docetaxel in a xenograft model devoid of any side effects on the mice (Makhov P, Golovine K, Canter D, Kutikov A, Simhan J, et al., 2012).

Hepatoprotective activity of black pepper:

It was found that piperine inhibited the increased level of serum GPT and GOT in dose-dependent manner in a hepato-toxicity model of mice caused by D-galactosamine. The hepatoprotective activity of methanolic extract of *Piper nigrum* fruits was evaluated in ethanol- CCl4 induced hepatic damage in Wistar rats. Ethanol-CCl4was used to induce hepatotoxicity in the rats. Prophylactic treatment with methanolic extract of *Piper nigrum* at a dose of 100 and 200 mg/kg body weight, p.o. and pre-treatment with piperine at a dose of 50 mg/kg body weight, p.o. for 15 days with Ethanol-CCl4 treatment rats showed significant liver protection as evidenced from the triglycerides levels, Alanine transaminase, Aspartate transaminase, alkaline phosphatase, bilirubin and superoxide dismutase, Catalase, Glutathione reductase and Lipid peroxidation levels to assess the liver functions. In this study, administration of Ethanol-CCl4 exhibited significant boost in triglycerides, Alanine transaminase, Aspartate transaminase, alkaline phosphatase, and bilirubin levels while there was significant decrease in the superoxide dismutase, catalase, and glutathione reductase levels which were restored to normal level after pre-treatment of methanolic extract of *Piper nigrum* and Piperine. Lipid peroxidations were also significantly decreased after pretreatment with methanolic extract of *Piper nigrum* and Piperine at given doses. The results were similar to that of reference standard-Liv52 at a dose of 1 mL/kg, p.o. for 15 days. The Morphological and histopathological studies of liver were also supportive of the biochemical parameters. Thus it is concluded that *Piper nigrum* possesses potential of hepato-protective activity due to the presence of piperine alkaloids and have great therapeutic potential in treatment of liver ailments (Nirwane A M, Bapat A R, 2012).

Antitussive and Bronchodilator:

Many traditional practices have proved it as well that *P. nigrum* is widely used in many herbal cough syrups due to its potent antitussive and bronchodilator properties (Majeed M, Badmeev V and Rajendran R, 1999). Many old people and herbal practitioners believed that the addition of little amounts of powdered peppercorn in a green tea significantly reduces asthma (Ahmad N, Fazal H, Abbasi BH, Farooq S, Ali M and Khan MA, 2012). 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(Kim SH, Lee YC,2009).

Anti-obesity Activity:

Obesity is becoming a global problem these days, 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 also. So, the experiments are now focusing on herbal medicine and other non-pharmacological ways 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 of them. In an antiadipogenesis 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 (Park UH, Jeong HS, Jo EY, Park T, Yoon SK, Kim EJ, Jeong JC and Um SJ, 2012). 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

(Shah SS, Shah GB, Singh SD, Gohil PV, Chauhan K, Shah KA and Chorawala M, 2011).

These results suggest that 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 wa 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 (Vijayakumar RS, Surya D, Senthilkumar R and Nalini N, 2002).

Digestive activity of black pepper:

Many spices are known for their digestive stimulant action. Dietary piperine enhances digestion by stimulation of the pancreatic enzymes and considerably decreases the food transit time of gastrointestinal tract. Piperine have been reported to increases the saliva production and gastric secretions, and increases the production and activation of salivary amylase. The oral administration of piperine or *P. nigrum* stimulates the liver to secrete bile acids which in turn play key role in the absorption and digestion of fats. The oral administration of active compounds like piperine, pipene, piperamines and piperamides significantly increases the activities of enzymes like pancreatic amylase activity, protease activity, lipase activity and chymotrypsin activation (Srinivasan K, 2007). An influence on digestive enzymes of intestinal mucosa was examined in experimental rats by Platel K and Srinivasan. The animals were fed with piperine (20 mg %) which significantly increased the activity of intestinal lipase, disaccharidases sucrase and maltase enzymes (Platel K, Srinivasan K, 1996). In another study, Platel K and Srinivasan evaluated the influence of piperine (20 mg %) on digestive enzymes of pancreas in experimental rats. Dietary piperine (20 mg %) significantly stimulated the activities of pancreatic lipase, amylase, trypsin and chymotrypsin (Platel K, Srinivasan K, 2000). The influence of some spices included in the diet, on food transit time was examined in adult female Wistar rats. Animals were maintained for 6 weeks on diets containing piperine (0.02 g %). The ferric oxide (0.5%) was included in the diet as an un-absorbable marker to monitor the food transit time. Time of

excretion of colored stool was noted to follow the time of consumption of the diet with the marker. The piperine (0.02 g %) significantly shortened the food transit time (Platel K and Srinivasan K, 2001).

Analgesic, Antipyretic and Anti-Inflammatory Activity:

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 (Sabina EP, Nasreen A,et al,2013). The experiment revealed the 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.

Immuno-modulatory activity of black pepper:

Immuno-modulatory and antitumor activity of piperine was evaluated. Piperine (250 µg/mL) was reported to be cytotoxic to Ehrlich ascites carcinoma cells and Dalton's lymphoma ascites. Piperine at a concentration of 50 µg/mL showed cytotoxicity to L929 cells in culture. Piperine administration also causes an increase in the total WBC counts in BAL b/c mice. Administrations of piperine were also reported to increase the bone marrow cellularity and alpha-esterase positive cells (Sunila ES, Kuttan G, 2004).

Antioxidant Activity:

Free radicals are responsible for causing many diseases. Different kinds of free radicals can attack on the cell membrane and alter membrane permeability, membrane damage, oxidation of lipids, loss of different enzymatic activities, and ultimately disrupt 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. 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 quantity. Plants are a potent source of antioxidant activity from ethno medicinal practices to today's findings. Many scientific findings prove its great antioxidant potency (Nahak G and Sahu RK, 2011). Piperine and *P. nigrum* maintain superoxide dismutase, glutathione peroxidase, catalase, glutathione-s-transferase, glutathione levels and reduce high fat diet induced oxidative stress (Vijayakumar RS, Surya D and Nalini N, 2004).

Effect of Piperine on metabolism: a bioavailability enhancer:

Piperine has shown bioavailability enhancing effects on many therapeutically important drugs and nutrients. Piperine increases the absorption of many drugs and nutrients from the gastrointestinal tract by various mechanisms. It alters the membrane dynamics and increases permeability at site of absorption. Piperine increases the serum half lives of some substances like beta-carotene and coenzyme Q10 and decreases metabolism of many drugs by inhibiting various metabolizing enzymes like cytochrome BS, CYP3A4, NADPH cytochrome, UDP-glucuronyl transferase, UDP-glucose dehydrogenase (UDP-GDH), and aryl hydrocarbon hydroxylase (AAH). These enzymatic inhibition by piperine resulted in increased bioavailability of many drugs and nutrients e.g. amoxicillin, ampicillin, acefotaxime, carbamazepine, ciprofloxacin, norfloxacin, metronidazole, oxytetracyclin, nimesulide, pentobarbitone, phenytoin, resveratrol, beta-carotene, curcumin, gallic acid, tiferron, nevirapine, and sparteine by different types of mechanisms. Therefore, piperine is known as bioavailability enhancer and a potent drug's metabolism inhibitor (Acharya SG, Momin AH and Gajjar AV, 2012).

Conclusion:

The human being used plants as the source of medicine since ancient time. Spices were part of these ancient traditional medicines. Until now, many drugs are obtained and produced from plants and natural products

and the majority of inhabitants still depend on the natural products (including spices) for their primary health care systems. Spices are used not only in food but also in medicine. The black pepper fruits (*Piper nigrum* L.) are the king of spices and used all over the world. This spice has many health benefits and used traditionally to treat different ailments. Numerous scientific studies, which have been summarized in this study, showed that the black pepper fruits have promising antibacterial activity,

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