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## Therapeutic Potential of Piperine: A Review

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**Abstract:** Piperine is an active compound of black pepper which is extracted from the plant *Piper nigrum* (family Piperaceae). Black pepper is a much popular spice for its pungent taste and widely used in different types of cuisine worldwide. Along with the application as spice, it is used in traditional medicine for many purposes. Piperine has enormous pharmacological activities like anti-cancer, anti-obesity, anti-inflammatory, neuroprotective and hypolipidemic effect in a dose dependent manner in various animals as well as in human. Piperine serves as a bioavailability enhancer and in combination with other drugs it multiplies the efficacy of that drug. Due to its various bioactive properties and physiological effects piperine can be used to treat many human health disorders. All these facts demonstrate the therapeutic potential of piperine. In this review we summarized a broad spectrum bioactive and therapeutic potentiality of piperine in different types of human diseases.

**Keywords:** Piperine, Alkaloid, Pharmacological effect, Bioavailability, Alternative drug

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## Introduction

Alkaloids are the secondary metabolites of the plants and are group of interesting small molecules which are abundantly available in Mother Nature. Many of the isolated alkaloids have unbelievable pharmacological properties that may contribute as a revolutionary for the progression of the humanity. Conventionally, human utilized alkaloids from several decades as medicine and the most prime among them are morphine, atropine, quinine, taxol, beta-carboline, barberine and so on. Piperine is a natural alkaloid which is

extracted from black pepper. *Piper nigrum* is a shrub which belongs to the family Piperaceae under the class Magnoliopsida. It is vigorously cultivated in tropical regions. Due to its strong aromatic flavors and causticity, it seems as the 'King of Spices' and it has important valuable medicinal effectiveness. It has a distinguishing essence due to the presence of an alkaloid piperine, along with volatile oils, and essential oils (Tiwari *et al.*, 2020). The piperine content differs from 2% to 7.4% according to the plant (Black

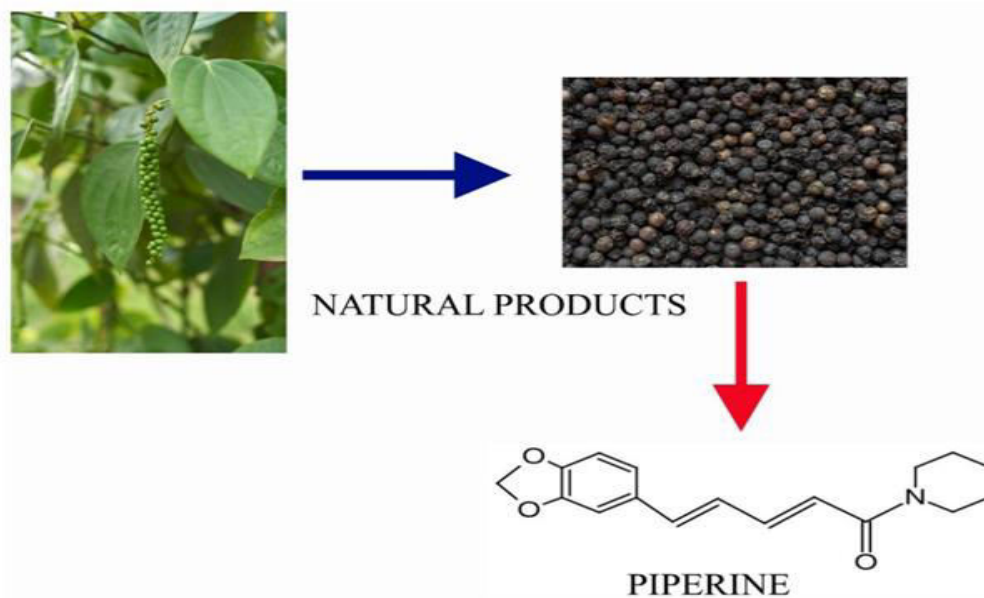


Fig. 1: Chemical structure of piperine.

pepper and long pepper). However, some reports indicate a high content of piperine up to 9% in black pepper and 4-5% in long pepper (Chopra *et al.*, 2016).

It is one of the common kitchen spices all over the world and famous for its strong chemical piperine (1-peperoyl piperidine, Fig. 1) which was discovered by Hans Christian (1819). Piperine is an alkaloid and its molecular weight is 285.34 Daltons with the formula  $C_{17}H_{19}NO_3$ . Piperine has a potent role against rheumatism arthritis, influenza and fever (Parthasarathy *et al.*, 2008). Piperine also enhances blood circulation (Taqvi *et al.*, 2008), salivation, and stimulation of appetite. Piperine has a diverged biological profile that contains pain management (Correaa *et al.*, 2008), anticancer activity (Pradeep and Khuttan, 2002), Hypotension (Obloh *et al.*, 2013) and vascular cell modulation (Hlavačková *et al.*, 2011). It has a role on many enzyme systems (including p-glycoproteins) (Meghwal and Ghoswami, 2013). Piperine has many biological activities such as anti-obesity, anti-inflammatory, anti-hypertensive, antioxidant, anti-platelets, antitumor, antifungal,

antibacterial, anti-amoebic, antiulcer, and antidepressant etc. (Su, 1977; Miyakado *et al.*, 1979; Mujumdar *et al.*, Ghosal *et al.*, 1996; 1990; Bang *et al.*, 2005; Lee *et al.*, 2005; Storz, 2005; Mehmood and Gilani, 2011; Tavaras *et al.*, 2011; Zarai *et al.*, 2013).

We independently searched (February 2020 to September 2021) from different search engines like Research Gate, ScienceDirect, PubMed, Google Scholar, Web of Science, Scopus etc. and explored different publications related with the biological effects of the natural alkaloid piperine. The study focuses towards the different pharmacological effects of the novel alkaloids piperine.

#### PHARMACOLOGICAL PROPERTIES OF PIPERINE:

Piperine has a vast range of biological activities; many of them have been proved by *in vivo* and *in vitro* studies. Piperine constitutes three sites such as (i) Side chain consists of conjugated double bonds; (ii) Methylenedioxyphenyl (MDP) ring; and (iii) Basic moiety is attached by carbonyl amide linkage to the side chain which are responsible for many bioactivities (Chopra *et al.*, 2016).

### Antioxidant activity:

Free radicals are the underlying cause behind several diseases. Several types of free radicals can attack the cellular membrane which in turn cause membrane damage, aging, loss of enzymatic functions or alter cell membrane permeability, lipid oxidation and eventually interrupt with proper cellular function and body physiology, which may lead to cancer. The free radicals, normally produced at the time of metabolism, are scavenged by several antioxidant of our body.

Superoxide anion radical scavenging activity of piperine (64.2% inhibition at concentration 75 µg/ml aqueous solution) was observed in an *in vitro* experiment performed by Takooree *et al.* 2019. DPPH1 (1-Diphenyl-2-picryl-hydrazyl) assay is performed to evaluate the antioxidant activity (Yamaguchi *et al.*, 1998). By this assay it was reported that 10.28% inhibition occurred at 50 µg/ml ethanolic extraction (Zarai *et al.*, 2013). It was reported that methanolic extract of *Piper nigrum* showed DPPH scavenging activity at 144.1 µg/ml concentration (Khalaf *et al.*, 2008). An *in vivo* experiment carried out on male Wistar rat reported that piperine (0.02 g/kg b.w.) has antioxidant properties which reduce TBARS (Thiobarbituric acid reactive substances) and CD (Conjugated dienes) to maintain the level of Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), Glutathione-s-transferase (GST) near the control rats (Vijaykumar *et al.*, 2004). Vijaykumar *et al.* (2006) reported that piperine improved antioxidant activity in male Wistar rat at a dose of 40 mg/kg body weight. Evidenced suggested that piperine has protective role against oxidative stress at a dose of 10 mg/kg/day for 14 days piperine treatment in Sprague-Dawley rats as diabetic model (Rauscher *et al.*, 2000).

### Anticancer activity:

Nowadays cancer is becoming a global threat in the modern civilization. There are certain systems present to combat with this disease like chemotherapy, radiation but we have to find an

alternative path which is significant as well as have less therapeutic side effects. So, in search of the new track, we found that herbal medicines have a significant role against cancer. Among these piperine also has anticancer and antitumor property.

Nowadays anticancer role of piperine is explored a much. Evidence through MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay showed that piperine re-sensitized P-glycoprotein, Breast Cancer Resistance Protein (BCRP) and multidrug resistance-associated protein 1 (MRP1) dependent resistant cancer cells (Li *et al.*, 2011). *In vitro* study revealed that after 24 h exposure IC<sub>50</sub> value is 1.21 µM on MCF-7 cell line (Motiwala and Rangari, 2015). Piperine has anticancer activities on human prostate cancer cell like DU145, LNCaP, PC-3 with a IC<sub>50</sub> value is 226.6 µM, 74.4 µM and 111.0 µM, respectively (Ouyang *et al.*, 2013) and inhibited cell proliferation. Piperine treatment (50 mg/kg body weight) showed the suppression of benzo(a)pyrene(B[a]P) induced lung cancer in male swiss albino mice (Selvendiran *et al.*, 2006). Piperine reduces 95.2% tumor nodule formation in C57BL/6 mice. Interestingly on B16F-10 melanoma cell piperine is 100% cytotoxic at a concentration of 100 µg/ml (Pradeep and Khatun, 2002). Piperine free *P. nigrum* extract show various anticancer effect (IC<sub>50</sub> of MCF-7 is 7.45 µg/ml, ZR75 is 13.85 µg/ml, MDA-MB-231 is 22.67 µg/ml) on various cell line through MTT assay (Sriwariyajan *et al.*, 2016). Evidence showed anticancer activity of piperine against 22RV1, LNCaP, DU-145 and PC-3 cell lines at a dose dependent manner and inhibit cell proliferation and annexin-v staining FITC (Fluorescein isothiocyanate) revealed piperine treatment induced apoptosis (Samykutty *et al.*, 2013).

### Neuroprotective role:

Many reports showed that piperine is a potent neuroprotector concurrently nerve stimulants also. It has been evidenced that piperine can stimulate central nervous system in different animal model (Chopra *et al.*, 2016). Piperine



diminishes MPTP induced motor coordination defects on Male C57BL/6 mice model (Yang *et al.*, 2015). Such evidence showed that piperine may take part in neuro-regulation by secretion of neurohormones mainly epinephrine (Kawada *et al.*, 1998). *In vivo* study in male Wistar rat revealed that reduction of locomotion activity of 6-OHDA groups was altered and the motor deficiency of 6-hydroxydopamine (6-OHDA) groups was completely inverted by treating with piperine (Correia *et al.*, 2015). Evidences have been presented to explain the role of piperine as neuroprotector. Pany *et al.* (2016) reported that piperine administration expanded the GSH level, brain plasma phenytotintratio, and viable neuron numbers and declined catalase activity and lipid peroxidation. Piperine also has an effective role in cognitive disorder and mood (Wattanathorn *et al.*, 2008). In combination with quercetin, piperine improved behavioral abnormalities in 1-Methy-4-phenyl-1,2,3,6-tetrahydropyridine treated rat and considered as a good neuroprotector.

#### *Hypoglycemic and hypolipidemic activity:*

Diabetes mellitus (DM) is a common problem in the health system. DM mainly occurs by declination of insulin or become insulin resistance followed by pancreatic  $\beta$  cell dysfunction. Evidence revealed that most of the patients diagnosed with DM are found to be hyperlipidemic. Hyperlipidemia and Type 2 Diabetes is correlated with each other.

Earlier study revealed that 4 weeks treatment with *P. nigrum* reduced blood glucose level in male albino rat (Kaleem *et al.*, 2005). Piperine supplementation with High Fat Diet (HFD) declined the level of plasma LDL, VLDL, total cholesterol, tissue HMG CoA reductase activity (Vijaykumar and Nalini, 2006). It also evidenced that after treatment of piperine at a dose of 20 mg/kg body weight can reduce free fatty acids, triglycerides, phospholipids, and total plasma cholesterol level and raise HDL level (Vijaykumar *et al.*, 2002). An *in vivo* study was performed with alloxan treated mice model showed a blood glucose lowering effect at a dose of 20 mg/kg body

weight (Atal *et al.*, 2012). Choi *et al.* (2013) showed that piperine treatment at a dose of 50 mg/kg b.w. reduced body weight and hepatic lipid concentration and improves insulin resistance in HFD –fed mice. Piperine treatment at a dose of 30 mg/kg body weight downregulates the lipogenes in visceral adipose fat (Du *et al.*, 2020). *In vivo* study in Sprague Dawley rats revealed that piperine has mitigating efficacy on HFD fed rat at a dose of 40 mg/kg body weight (Brahma Naidu *et al.*, 2014). Piperine supplementation also increases HDL and vitamin C levels in pigs (Yang *et al.*, 2019).

#### *Hypotensive effect:*

Hypertension is considered the utmost vital factor for developing vascular disease. There are many medicines available in the market which helps to reduce hypertension or control it. But this is not the solution, we have to choose some alternative method to get rid of it. Some medicinal plants have a crucial role to control hypertension. Among them *P. nigrum* has a hypotensive activity.

Early report disclosed that piperine enhanced the plasma NO concentration which promotes vasorelaxation in L-NAME (N $^{\omega}$ -Nitro-L-arginine methyl ester hydrochloride) induced hypertensive rats (Kumar *et al.*, 2010). Piperine also possesses calcium channel blockade effect and lowers Blood pressure within a limit (Taqvi *et al.*, 2008). This alkaloid showed a significant decrease in mean arterial pressure and myofibril content and increase actin (Hlavačková *et al.*, 2011). Piperine act as vasorelaxants in L-NAME induced hypertensive rat and partially decrease blood pressure (Booranasubkajorn *et al.*, 2017).

#### *Anti-inflammatory activities:*

Piperine is a potent anti-inflammatory agent. Study revealed that piperine exhibited maximum activity on paw edema at a dose dependent manner. Piperine possesses analgesic and anti-inflammatory effect by tail immersion and carrageen induced paw edema assay at a dose of 5 mg/kg and 15 mg/kg body weight, respectively (Tasleem *et al.*, 2014). It has been reported that

piperine inhibited the proinflammatory factors, MMP13 (matrix metalloproteinase 13) in arthritis rat model (Bang *et al.*, 2009). Piperine shows anti-inflammatory activities in chronic and acute experimental models like cotton pellet granuloma, rat paw edema etc. (Majumdar *et al.*, 1990). Piperine manifests anti-inflammatory effect in arthritis induced by adjuvant at a dose of 30 mg/kg body weight and returned to normal level (Murunikkara *et al.*, 2012). In rats administration of lead acetate induced an elevation of creatinine and blood urea nitrogen levels, indicating its potential to impact renal function. Moreover, piperine has a nephroprotective effect in this context (Sudjarwo, *et al.*, 2017). Many studies showed that piperine can reduce inflammatory markers, IL-1 $\beta$  and TNF- $\alpha$  in Parkinson's rat model induced by 6-OHDA (Shrivastava *et al.*, 2013).

#### *Antimicrobial effect:*

Anti-microbial agent means which inhibits the growth of micro-organism or kills them. From the past decades many plants or phytochemicals are used as antifungal, antibacterial or pesticide etc. Many evidences proved the anti-microbial property of piperine. It has been reported that piperine possesses a synergistic effect with Ciprofloxacin at a concentration of 20  $\mu$ g/ml on *Escherichia coli* and *Bacillus subtilis* (Maitra and Shilpi, 2017). Many progressive data are also present against piperine. A synergistic effect was also observed with a combination of Tetracycline and Piperine on *Staphylococcus aureus* (Mgbeahuruike *et al.*, 2019). Piperine has very potent anti-bacterial property against gram +ve and gram -ve bacteria by the inhibition of Nor A efflux pump which is responsible for the release of toxic substances. Piperine revealed highest effect against *Escherichia coli* and *Candida albicans* at an inhibitory zone of 20 nm and 23 nm diameter, respectively. Piperine inhibit the growth of *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* etc. with an inhibitory zone of 8.23- 18 nm measured by agar well diffusion method (Hikal, 2018). This alkaloid has anti-bacterial property

against gram +ve and -ve bacteria with a range of 8-23 nm ZOI (Zone of inhibition) (Aldaly, 2010). Ethanolic extract of *P. nigrum* shows anti-bacterial role against *Bacillus subtilis*, *Staphylococcus aureus* with a MIC (Minimum inhibition concentration) value of 156.25 mg/ ml (Zarai *et al.*, 2013). Petroleum ether extraction of *P. nigrum* reported as most effective against *Klebsiella aerogenes*. and *Bacillus subtilis* at a concentration of 100  $\mu$ g (Reddy *et al.*, 2004) and acetone extraction did not show any kind of inhibition of any microorganisms (Maitra and Shilpi, 2017).

#### *Bronchodilator and antitussive effect:*

From ancient time black pepper is widely used as potent bronchodilator. So in Ayurveda or traditional herbal medicine it is used in cough syrups. The experiment revealed that this alkaloid act as Ca<sup>++</sup> channels blockade and inhibition of Phosphodiesterase which help to reduce respiratory problems (Rehman *et al.*, 2008). Piperine suppressed the allergic inflammation by inhibition of Th2 cytokines, histamine and IgE production and treated asthma in Balb/c model (Kim and Lee, 2009). Study revealed that in guinea pigs with combination of peptic polysaccharides piperine (50 mg/kg bw) enhances antitussive effect (Khawas *et al.*, 2017).

#### *Anti-obesity activity:*

Obesity is a burning problem in this world due to uncontrolled fat accumulation and this leads to severe chronic disorders such as hypertension, cardio-vascular diseases, fatty liver, dyslipidemia, insulin resistance and osteoarthritis. There are various drugs available in the market to control obesity, but we need to find out some herbal medicine which has less side effects.

Previous study suggested that piperine supplementation altered the body weight, fat percentage, glucose level, lipid profiles in a rat model with HFD induced obesity (Brahma Naidu *et al.*, 2014). Piperine also reduced body weight and plasma total lipid content, VLDL, LDL, TG and TC but increased HDL at a dose of 40 mg/kg body weight in a HFD induced Obese Rat model (Shah *et*

*al.*, 2011). Experiment revealed that piperine inhibited adipocyte cell differentiation by down regulation of PPAR $\gamma$  (Peroxisome proliferator-activated receptor gamma) activity as well as repressed the PPAR $\gamma$  expression (Park *et al.*, 2012). In HFD induced obese mice it was found that piperine downregulated the mRNA expression in visceral adipose tissue and subcutaneous adipose tissue at a dose of 30 mg/kg body weight (Du *et al.*, 2020). *In vitro* studies of Oboh *et al.* (2013) revealed that Piperine inhibited the Angiotensin converting enzyme (ACE) in a concentration dependent manner. These activities suggest piperine as a cardio-vascular protective agent also.

#### *Digestive and hepatoprotective activity:*

Many research findings exhibit the digestive and hepatoprotective role of *P. nigrum* as well as its active alkaloid piperine in human and animal model also. Piperine showed promising hepatoprotective effect on Acetaminophen-induced hepatotoxic mice which in turn decreased TNF- $\beta$ , liver marker enzymes activity (Sabina *et al.*, 2010). Study revealed that 50 mg/kg body weight of piperine treatment alters the liver biochemical parameters in hepatotoxic rat induced by Ethanol-CCl<sub>4</sub> treatment and histological studies supported the data (Nirwane and Bapat, 2012). Piperine amplified the release of digestive enzymes, saliva and decreased the GI food transit time (Srinivasan, 2007). Piperine supplementation with diet may increases efficiency of trypsin by 120%. It also influences amylase, lipase, and chymotrypsin (Patel and Srinivasan, 2000).

#### *Anti-fertile effect:*

Nowadays population outburst is a major issue to the society. We have to control population because our resources are limited, and this results the scarcity of food shelter and socio-economic problem arise for this. Our population control concept based on female but we should think the male alternative, a suitable male contraceptive which have less side effects. Piperine can be a

good alternative for male oral contraception. Piperine altered serum FSH level, imbalance sex hormone, testicular testosterone level but this imbalance restored after withdrawal period (Chinta *et al.*, 2017). Experimental findings suggested that piperine damaged epididymal sperm DNA of goat and decrease the sperm viability and motility. This activity may consider piperine as a potent anti-fertile agent (Chinta *et al.*, 2014). Piperine plays an antagonist role to dihydrotestosterone and binds with androgen receptor which results an effective male contraceptive agent (Chinta *et al.*, 2015).

#### *Piperine as bioavailability enhancer:*

Bioavailability enhancer means a molecule which is not act as drug but in combination with a drug it manifest drugs metabolism several times or increase the absorption across the membrane and enhance the drugs bioavailability. Many reports suggest that piperine act as bioavailability enhancer either by detaining the metabolism of the drug or expanding the absorption (Singh and Deep, 2011). Research findings proposed that piperine acts in multiple ways including cell signaling pathway modulation, receptor binding capacity and inhibition of drug pump efflux (Bajad *et al.*, 2001). Piperine interestingly increases the drug absorption in Gastro-intestinal tract, when it passes through liver (Kesarwani and Gupta, 2013). Atal *et al.* (1985) reported that oral gavage of piperine inhibited UDP-glucuronyltransferase and hepatic arylhydrocarbon hydroxylase. Ampicillin and Norfloxacin have low oral bioavailability but it had been showed that 20 mg/kg co-administration of piperine amplified the oral bioavailability of these drugs (Janakiraman and Manavalan, 2008).

#### **Conclusion**

The present review on the pharmacological effect of the alkaloid piperine merged towards pharmaceutical excellence of the piperine in a single frame (Fig. 2). Piperine has significant medicinal values such as analgesic, anti-inflammatory, anticancer, anti-obesity, hypoglycemic, hypolipidemic and neuroprotective

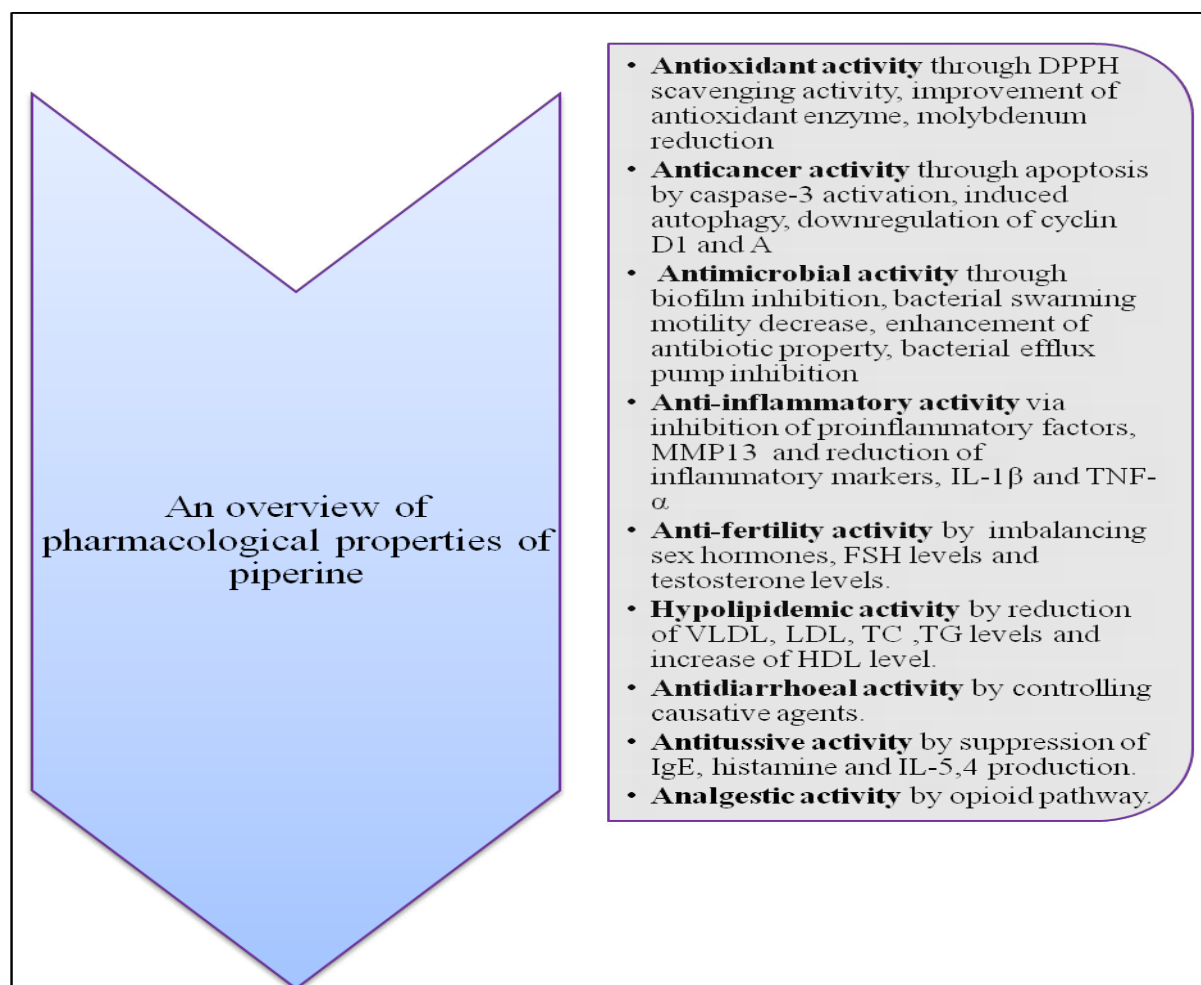
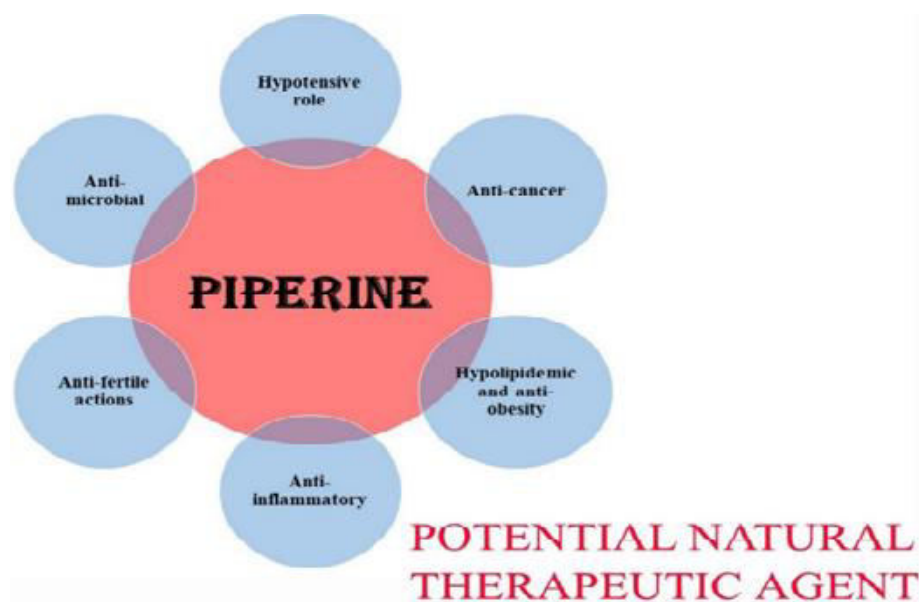


Fig. 2: Pharmacological activity of piperine and different mode of action.



role. Though there are extensive studies on the pharmacological effects of piperine on the above mentioned functions, however, there are still some lacunae on its effect on cardio-vascular diseases (CVDs) and hypertension. Piperine also has cardio-vascular protective effect still some gap is present like piperine helps to inhibit or reduce atherosclerosis but there is no distinct evidence against it. Piperine act as vasorelaxant in L-NAME induced hypertension but there are many other reasons of hypertension, this area still not discovered in details. However, modern science innovates new methods of application, synthetic modifications, nano-encapsulation to focus the exact mechanism of action of Piperine and investigations are required for its toxicity test, standardization and clinical trial. Natural alkaloids have enormous pharmacological efficiency without showing little or no toxicity rather than chemical synthetic drugs. It will be more useful if we get a better replacement of chemical synthetic drugs because piperine is tremendous potent in many sectors and its therapeutic utilization will be beneficial in severe therapies and treatments. The utmost acknowledgment of all such research findings mainly supports to develop more advanced drugs based on natural years on above mention fields for better therapeutic applications.

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