ISSN: 2287-688X

Annals of
Plant Sciences

Volume 10, Issue 4 (2021) pp. 4180-4194

Review Article

A review on Traditional usage, Phytochemistry, Anticancer molecules of *Piper nigrum* L. (Indian Pepper)

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Abstract: *Piper nigrum* L. is a historic spice yielding plant and its fruit forms an integral part of human diet. It comprises of versatile molecules with prime pharmacological actions and therapeutic use including those that are very promising for the combat of dreaded disease such as cancer. Piperine, pellitorine and piperidine are important antitumor molecules present in the plant that are ideal for inclusion in the battery of approaches in cancer therapy. This plant may still be explored considering the medicinally important biomolecules inherent in it. This study was aimed at making a systematic review with regard to data on traditional uses and pharmacological attributes of the biomolecules that are present in the plant, particularly those having antitumor potentiality.

Keywords: *Piper nigrum*, antitumor, anticancer, piperine, pellitorine, piperidine.

Introduction

The genus *Piper* (Family: Piperaceae) comprises of over thousand species that are distributed primarily in the pantropical regions of the world (Chaveerach *et al.*, 2006). Active metabolites of the nature of mainly alkaloids and amides that are secondarily formed and having great medicinal values are largely present in this genus (Chowdhury and Baruah, 2020). A well-known species belonging to this genus is *Piper nigrum* L.(Figure 1). It is a perennial evergreen woody herb that can climb to the extent of 10 m or more and producing small round berry-like single seeded fruits borne in spikes that turn red on ripening (Damanhouri and Ahmad, 2014).

Piper nigrum is an export-oriented spice crop richly laden with essential oil and oleoresin. This taxon is one of the oldest spices that is known to mankind and is also the most widely utilized spice in the world (Ashokkumar *et al.*, 2021). For its wide culinary application and volume of its trade, it has reputedly come to be called as "The king of spices" (Damanhouri and Ahmad, 2014). Its spiciness or pungent taste is attributed to the presence of alkaloid, piperine (Stoja-novic-Radic *et al.*, 2019).

Figure 1. *Piper nigrum* L.

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Piper nigrum accounts for about 35% of the total spice trade going round the world. Besides being a principal spice, the plant has potency for food preservation (Nakatani *et al.,* 1986) and is commonly used for seasoning of food (Li *et al.,* 2020). Essential oil present in the plant confers it a characteristic aroma (Sruthi *et al.,* 2013) that has ensured its commending application in perfume industry. *Piper nigrum* is also useful as an insecticide (Srinivasan, 2009). Most importantly, the plant is gifted with enormous medicinal properties that have been known to societies round the globe ever since the start of human civilization (Orav *et al.,* 2004).

Medicinal richness of this plant is because of heavy load of phytochemicals in the form of secondary metabolites present in the plant (Srinivasan, 2007; Ahmad *et al.,* 2012). Fruit of *P.nigrum* is commonly used for medicinal and other purposes. Its fruit that is commonly called as 'pepper', is known by different names. In Urdu and Hindi *P. nigrum* fruit is said as Kali Mirch, Pippali in Sanskrit, Milagu in Tamil, in English language fruit is called as Peppercorn, Green pepper, White pepper, Black pepper or Madagascar pepper (Damanhouri and Ahmad, 2014). Harvesting of the fruit is carried out at different stages of maturity. Unripe fruits yield green pepper, ripe fruits yield black pepper, while ripe fruits after getting rid of the flesh and outer skin yield white pepper (Orav *et al.,* 2004).

P. nigrum is considered to have originated in the Malabar Coast from South-western segment of India. From this center of its origin, it is considered to have spread to other parts of the world. The plant is presently on commercial scale cultivation in the tropics and today, India, Indonesia, Brazil, Malaysia, Thailand, Sri Lanka, Madagascar, Mexico are some of the leading countries engaged in commercial scale cultivation (Salehi *et al.,* 2019). This plant can thrive in varied conditions of soil, climate and altitude, although hot and humid climate is the most preferred.

This paper reviewed traditional knowledge associated with this spice of repute along with *in vitro* and *in vivo* studies with regard to active biomolecules showing anticancer potentiality.

Traditional use of *Piper nigrum*

Mankind has come to know and used good number of plants for their health reasons since very early period. Medicinal plants have stood to be a significant source of natural remedy against various ailments. There are different medicinal systems being practiced by the mankind since ancient times called as traditional system of medicine or ancient system of medicine. Several literatures concerning such ancient medicinal systems that date back to very early period are available. However, even today there are several ancient systems of medicine that are mostly practiced by the natives and have continued as oral pharmacopoeia transmitted over generations by word of mouth (Majumdar *et al.,* 2019). But in recent times systematic investigations have been undertaken and this coupled with technological advancements have given newer insights and ancient systems of medicine have greatly improved. Such systems of ancient medicine have evolved over millennia of existence of human civilization (Salehi *et al.,* 2018; Sharifi-Rad *et al.,* 2018).

Ancient or traditional medicines are relatively much cheaper but at the same time are very effective and regarded to be safe without side effects because of its natural origin. Traditional medicines that are being used generally by the lesser privileged people are now a days followed by those who have easy access to modern medicines (Anquez-Traxler, 2011). Ancient medicinal systems such as Ayurveda, Unani, Siddha as well as folk medicine of several countries round the globe are known to have used pepper for the purpose of prevention and cure

of several ailments. Existing literatures concerning ancient systems of medicine have nicely documented versatile properties of pepper (Srinivasan, 2009, Ahmad *et al.,* 2014). Pepper is said to give cure to variety of ailing conditions according to Ayurvedic system of medicine, particularly the gastrointestinal disorders (Chopra and Chopra, 1959; Akamasu, 1970; Handbook of domestic medicine and common Ayurvedic remedies, 1979; Perry, 1980).

In Ayurveda, the combination of *Piper nigrum, Piper longum* and ginger is together called as 'trikatu', is widely used for preparation of different medicines effective against varied ailing condition. 370 different Ayurvedic formulations appear in the handbook of domestic medicines and common ayurvedic remedies that is said to give effective remedy from different ailments (Handbook of domestic medicine and common Ayurvedic remedies, 1979). Out of this total of 370, formulation numbering 210 comprises of either *P. nigrum* alone or the combination called as 'trikatu'. Ayurvedic formulations containing *P.nigrum* has been used for intermittent fever, disorders related to the pulmonary and gastrointestinal tract and helps to promote bile secretion (Majeed and Prakash, 2000). Reference of use of pepper for treatment of diseases like cholera, dyspepsia, flatulence, diarrhoea, gastrointestinal disorder, throat and oral problems, skin disease, piles, gonorrhea, night blindness, chest pain, diphtheria, alopecia are to be found in Unani literatures (Nadkarni, 1976).

Different folk medicine systems are being practiced round the globe. India tops the list of countries with highest report of traditional use of *P. nigrum*, mostly for menstrual, ear, nose and throat related disorders in case of human and for the correction of gastrointestinal problems of livestock (Takooree *et al.,* 2019). Since ancient times Black pepper has served as traditional cure against cuts and wounds (Ashokkumar *et al.,* 2021), fever, neurological and bronchopulmonary disorders (Majeed and Prakash, 2000). According to folk medicine system of Cambodia, pepper can give cure from dysen-tery, while pepper combined with other local herb can exert birth control (Kritikar and Basu, 1987). Traditional herbal healers of Thailand recommend pepper for the cure of cold, fever, headache, asthama, skin problems, abdominal fullness, abdominal tumors, kidney stone, malaria, stomach ache, adenitis, cancer, cholera, colic and for abortion (Chaveerach *et al.,* 2006). Pepper finds use for correction of conditions like headache, muscular pain, rheumatism, throat infection, influenza and improvement of human blood circulation according to traditional Chinese medicine (Gorgani *et al.,* 2017). Antiepilepserine, an analogue of piperine and an antiepileptic drug developed by Chinese researchers is based on the use of black pepper for the treatment of epilepsy by traditional Chinese healers (Majeed and Prakash, 2000). Traditional Chinese healers use pepper in some formulation in order to treat cancers of respiratory tract and abdomen (Chen, 2008). There is reference of use of pepper as tranquilizer and as antiemetic in accordance with traditional Chinese medicine (Salehi *et al.,* 2019). Pepper is major component of medication that is used for treatment of stroke in accordance with Traditional Chinese Hui Medicine (Liu *et al.,* 2011; Li *et al.,* 2013a; Li *et al.,* 2013b; Luo *et al.,* 2014; Zhang *et al.,* 2014) that is an integration of traditional Chinese medicine and Arab medicine. Black pepper has been used as a nerve tonic in accordance to traditional Middle Eastern medicine (Majeed and Prakash, 2000).

Different parts of *Piper nigrum* and its active components have been put to extensive in vitro and *in vivo* experimentation in order to test their efficacy and biological role have been evaluated showing great promise. Phytochemi-

cals obtained from pepper have showed wide range of pharmacological activities such as anti-inflammatory (Abdel-Daim *et al.,* 2019), antioxidant (Favre *et al.,* 2020), antiglycation (Favre *et al.,* 2020), anti-cancer (Jafri *et al.,* 2019), larvicidal (Ahmad *et al.,* 2020), anticariogenic (Dwivedi and Singh, 2016), antifungal (Castellanos *et al.,* 2020), antibacterial (Umadevi *et al.,* 2018), antiviral (Maurya *et al.,* 2020), antidiarrhoeal (Bajad *et al.,* 2001), antiplatelet (Son *et al.,* 2014), antihypertensive (Taqvi *et al.,* 2008), antiasthamatic (Parganiha *et al.,* 2011), anticonvulsant (Mao *et al.,* 2017), antimalarial (Thiengsusuk *et al.,* 2018), immunomodulatory (Majdalawieh and Carr, 2010), neuroprotective (Manap *et al.,* 2019), hepatoprotective (Rathee *et al.,* 2018), Antihyperglycemic (Wang *et al.,* 2020), antigentoxic (Verma *et al.,* 2017) and antithrombotic (Saleem *et al.,* 2019) besides host of several others. Such findings validate and strongly support existing traditional systems of medicine.

Phytochemical profile of *Piper nigrum* L.

There is always a continued need for search of new and safe drugs that can give remedy from common to chronic ailments. In this arduous search for new drugs, plants have always been a good source for natural chemical compounds with potentiality to fight against diseases (Newman and Cragg, 2012). Owing to large-scale use of *P. nigrum* in several ancient medicinal practices in different parts of the world combined with other economic utilities, the plant is resorted to intense phytochemical screening. Such studies have come up with presence of array of compounds viz. phenolics, flavonoids, alkaloids, amides, steroids, lignans, neolignans, terpenes, chalcones etc. (Pino *et al.,* 2003; Abbasi *et al.,* 2010; Khusbu *et al.,* 2011; Kumar *et al.,* 2013; Ganesh *et al.,* 2014; Pelayo *et al.,* 2016), alkaloids and amides being the prime component.

P.nigrum has been a rich reservoir of essential oil like most other species of the genus. This essential oil is a mix of different class of volatile chemical compounds. The content of essential oil was found to be in the range of 0.359% to 2.25% (Li *et al*., 2020). It varies from colourless to dark green to yellowish green in colour (Li *et al.,* 2020). However, colour, concentration and composition of essential oil differs depending on the chemotype, geographical location, considered plant part, soil, growing season, environmental condition, harvesting time, maturity of the plant, processing mode and the method that is adopted for extraction of the oil (Burt, 2004; Li *et al.,* 2020). Chemical constituents numbering more than hundred have been reported from *P.nigrum* essential oil (Narayanan, 2005). A list of major constituents of *P. nigrum* essential oil is shown in Table 1 (Mohammed *et al.,* 2016; Vinturelle *et al.,* 2017; Dosoky *et al.,* 2019; Andriana *et al.,* 2019; Salehi *et al.,* 2019). Pepper essential oil mainly consti-tutes monoterpenes and sesquiterpenoids having different structures (Huan and Long, 2007), monoterpene hydrocarbons (47–64%) being dominant over sesquiterpene hydrocar-bons (30–47%) (Zacharia and Gopalam, 1987).

Table 1. A list of major constituents of *Piper nigrum* fruit essential oil (Mohammed *et al.,* 2016; Vinturelle *et al.,* 2017; Dosoky *et al.,* 2019; Andriana *et al.,* 2019; Salehi *et al.,* 2019).

Compound	Molecular formula	Molecular weight (g/mol)
Monoterpene hydrocarbons		
α-Pinene	$C_{10}H_{16}$	136.23
β-Pinene	$C_{10}H_{16}$	136.23
α-Thujene	$C_{10}H_{16}$	136.23
β-Thujene	$C_{10}H_{16}$	136.23
σ-Ocymene	$C_{10}H_{16}$	136.23
δ-3-Carene	$C_{10}H_{16}$	136.23
Limonene	$C_{10}H_{16}$	136.23
Sabinene	$C_{10}H_{16}$	136.23
α-Phellandrene	$C_{10}H_{16}$	136.23
β-Myrcene	$C_{10}H_{16}$	136.23

p-Cymene	$C_{10}H_{14}$	134.21
Terpinen-4-ol	$C_{10}H_{18}O$	154.25
Sesquiterpene hydrocarbons		
(E)-β-Farnesene	$C_{15}H_{24}$	204.35
β-Bisabolene	$C_{15}H_{24}$	204.35
α-Humulene	$C_{15}H_{24}$	204.35
(E)-β-Caryophyllene	$C_{15}H_{24}$	204.35
α-Copaene	$C_{15}H_{24}$	204.35
α-Cubebene	$C_{15}H_{24}$	204.35
δ-Elemene	$C_{15}H_{24}$	204.35
β-Elemene	$C_{15}H_{24}$	204.35
Trans-Bergamotene	$C_{15}H_{24}$	204.35
Trans-Muurola-4(14),5-Diene	$C_{15}H_{24}$	204.35
Caryophyllene oxide	$C_{15}H_{24}O$	220.35

Anticancer molecules of *Piper nigrum*

Anticancer potentiality of plant-derived phytochemicals has become the focus of the scientific community undergoing recommendable works in this area (Landis-Piwowar and Iyer, 2014). Plant based molecules are regarded to be safe with least side effects as against various kind of toxicities encountered during the use of synthetic molecules (Desai *et al.*, 2008). *Piper nigrum* that is widely used as folk medicine including its application as an anticancer agent have attracted researchers from all over the world to come up with novel cytotoxic compounds that are considerably present in the plant and can counter this dreaded disease. Alkaloids and amides are major secondary metabolites present in *P. nigrum* in addition to myriad of several others (Chowdhury and Baruah, 2020).

Piperine, pellitorine and piperidine are such secondarily produced phytoconstituents prevalent in *P.nigrum* that have anticancer potentiality.(Figure 2 , 3, 4.)

Piperine.

Piperine (Figure 2) (1-Piperoylpiperidine) was first isolated in 1819 by Hans Christian Orsted, from the fruits of *Piper nigrum.* It is an important dietary alkaloid present in the plant (Zheng *et al.*, 2016) having broad spectrum therapeutic potentialities against wide range of disorders including cancer. It is regarded to be the main constituent of *P. nigrum* that is responsible for most of the therapeutic actions of the plant (Stojanovic-Radic *et al.*, 2019). Alkaloid component of the plant remains in the range of 2-9% of dry weight (Ravindran, 2003; Peter, 2006; Parthasarathy *et al.*, 2008). It is a yellow crystalline compound having melting point between 128-130°C and chemical formula $C_{17}H_{19}NO_3$ (Gorgani *et al.*, 2017). Several in vitro and in vivo studies have been made with regard to this dietary plant-based molecule, highlighting different modes of action that may largely come to the aid of cancer chemotherapy and radiotherapy at various stages of the disease (Rather and Bhagat, 2018).

Release of blocked apoptosis of misplaced and damaged cells is one of the primary targets of cancer treatment. It has been observed that piperine can activate cellular apoptosis via several pathways. LNCaP and PC-3 are two important and well-studied human-derived cancer cell lines used for prostate cancer research (Seim *et al.*, 2017). One way to check multiplication of cells is by hindering Voltage-gated K^+ channels of the plasma membrane (Wonderlin and Strobl, 1996). Targeting voltage-gated K^+ channels of LNCaP and PC-3 prostate cancer cell lines of human being using piperine showed potentially cytotoxic effect towards both the cell types, leading to seizure of cell cycle and cell proliferation (Ba and Malhotra, 2018). Under experimentation, piperine could bring down activetion of caspase-3 and mitochondrial membrane potential while bring an increase in the formation of reactive oxygen species (ROS) inhibiting the growth and proliferation of cervical cancer cells (HeLa) (Jafri *et al.*, 2019). Excess of reactive oxygen species (ROS) formation and Caspase-3 activation can cause persistent break in the DNA strand and initiate a cell dismantling process (Porter and Janicke, 1996; Circu and Aw, 2010).

Piperine can interact with DNA, it becomes potential for targeting this molecule towards specific DNA sequences for the purpose of control over gene expression that may help in regulation of cancer cell cycle. Piperine shows binding specificity towards sequences such as regulatory regions of oncogenes as that of c-myc that also have control over cellular apoptosis, growth and proliferation (Tawani *et al*., 2016). Such DNA binding ability of piperine becomes important in down regulation of pro-oncogenes and may also become helpful in development of anticancer drug that is DNA specific (Haris *et al*., 2015). During growth of tumors, formation of blood vessels or angiogenesis from the pre-existing ones gets uncontrolled leading to further growth and progression of the disease (Ria *et al*., 2010). Angiogenesis inhibitors fight cancer in an indirect way, *i.e.,* by targeting the blood supply and not the tumor cells depriving them of oxygen and nourishment (Doucette *et al*., 2013). Piperine was found effective in inhibiting collagen-induced angiogenic activity in cancer-induced animal model without bringing death of the cancer cells (Doucette *et al*., 2013). This was reported to be achieved by inhibition of prognostic cancer biomarker vascular endothelial growth factor (VEGF), a key contributor in the formation of new blood vessels. Anti-angiogenic therapy therefore can greatly boost standard cancer therapy in practice regulating the tumor vasculature (Duda *et al*., 2007).

Once the cancer had already developed it becomes very important to block cancer cell migration and metastasis development (Manayi *et al*., 2018). Piperine can reportedly bring in modification of various enzymes both at the level of transcription as well as translation and hinder migration of tumor cells and help avoid invasion of other tissues. Matrix metalloproteinase (MMP) or matrixinis a large protein family implicated in the degradation of extracellular matrix and are said to play major role in tumor aggressiveness and invasion (Lint and Libert, 2007; Xu *et al*., 2010). Piperine has been found to be effective in down regulation of matrix metalloproteinases and thereby inhibit migration of cancer cells and stop invasion in different animal models (Hwang *et al*., 2011; Lai *et al*., 2012).

Acquired drug resistance often pose significant challenges during treatment of cancer and are found to be associated with almost any cancer therapy that is given to combat the disease. Multidrug resistances (MDRs) encountered in cancer therapy may be attributed to drug efflux from the cells and drug metabolism (Szakacs *et al*., 2006). Natural compounds as that of piperine can reportedly inhibit efflux of potential anticancer molecules such as doxorubicin from drug resistant cell lines by inhibiting the activity of transmembrane protein P-glycoprotein (P-gp) and can therefore, ensure bioavailability of the drug in the targeted cancer cells (Li *et al*., 2018).

The extent of drug circulation and its availability in the targeted sites increases efficacy of the concerned drug and at the same time help in minimizing the dose required to achieve the therapeutic goal (Wen *et al*., 2015). Several types of bioenhancers are known that ensures maximal drug availability within tissues without having any side effect. Such an approach of ensuring maximal drug availability is equally important in cancer therapy (Randhawa *et al*., 2011). Piperine is the first scientifically validated natural bioenhancer (Atal and Bedi, 2010) that enhances availability of several therapeutic drugs. Resveratrol, a powerful antioxidant and a potential anticancer molecule is rapidly metabolized in the body (Wenzel and Somoza, 2005). However, piperine has been found to enhance plasma concentration of resveratrol (Johnson *et al*., 2011) and may go a long way in translating the virtues of such important molecules in the

favour of human beings. Piperine has shown potentiality of enhancing bioavailability of some other drugs such as sulfadiazine, tetracycline, streptomycin, rifampicin, pyrazinamide, isoniazid, ethambutol and phenytoin (Khan *et al.*, 2010; Verma *et al.*, 2011). Tetracycline, a common broad-spectrum antibacterial antibiotic reportedly has off target antitumor activity (Lokeshwar, 2011).

Pellitorine

Pellitorine (Fig. **3**) [(E,E)-N-(2-Methylpropyl) 2, 4-decadienamide] is a fatty alkamide. It is another important anticancer molecule found to be present in *Piper nigrum*. It is Yellow to beige solid with molecular formula $C_{14}H_{25}NO$ and melting point of 69^0C (Rosario *et al.*, 1996). This important plant phytochemical was first isolated by Gull and Hopton from roots of *Anacylus Pyrethrum* (Crombie, 1954). Like other wonder molecules present in *P. nigrum*, pellitorine have several attributes, *viz.* antiprotozoal, larvicide, antiseptic, antithrombotic, antituberculosis, antibacterial, antiplatelet aggregation, vascular barrier protective and anticancer (Ee *et al.*, 2010).

Pellitorine is lesser studied in comparison to piperine. However, in vitro studies have showed strong cytotoxicity of this plant-derived phytochemical against certain cancer cell lines revealing anticancer potentiality of this chemical molecule. Pellitorine exhibited strong cytotoxicity against human leukemia cell line (HL60) and breast cancer cell line (MCT-7) (Ee *et al.*, 2010). Level of toxicity of pellitorine was found to be more towards HL60 in comparison to MCF-7 cancer cell lines. Toxicity may also be due to synergistic influence on other biologically active molecules (Ee *et al.*, 2010).

Recent studies have documented that positive activation of TRPV1 ion channel can aid modulation of immune response and thereby help in treatment of inflammatory disorders and cancer (Bujak *et al.*, 2019). Pellitorine has been found to inhibit exovanilloid-induced pain by upregulation of TRPV1 ion channel (Olah *et al.*, 2017). This opens up a newer approach towards of cancer therapy.

Piperidine.

Piperdine (Fig. 4) is another cytotoxic molecule isolated from *P.nigrum* (Lim *et al.*, 2009). It is a heterocyclic amide, a colourless liquid with chemical formula $C_5H_{11}N$ and boiling point of 106°C. Piperidine offers optimal supramolecular interactions with various receptors of the cell and can support cancer therapy via several mechanisms of action (Goel *et al.*, 2018). In vitro studies conducted on Human epithelial type 2 (HEp-2) cancer cell lines elucidated cytotoxic efficacy of piperidine (Reshmi *et al.*, 2010). Piperidines were found to be potential scavengers of reactive nitrogen and oxygen species. They can bind to ctDNA and cause toxicity towards cancer cell lines and thereby inhibits their proliferation (Das *et al.*, 2017).

Figure. 2,3,4 : Phytoconstituents of *P.nigrum*

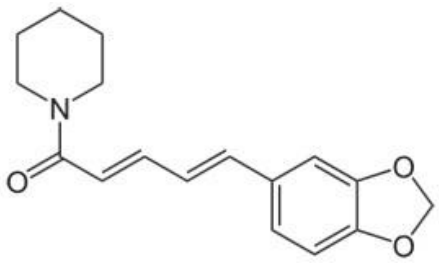

Figure 2. Piperine

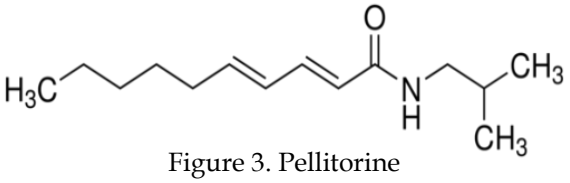

Figure 3. Pellitorine

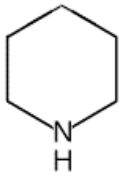

Figure 4: Piperidine

Efficacy of *Piper nigrum* derived molecules against clinical consequences of cancer.

Besides having direct influence on various types of cancer cells, piperine, pellitorine and piperidine may help to get rid of clinical issues that often arise in cancer related cases (Wojtukiewicz *et al.,* 2017). During cancer development and progression, inflammations of severe nature generally occur and it becomes necessary to deal with such situation.

Piperine and pellitorine have strong anti-inflammatory property (Ku *et al.,* 2014; Kumar *et al.,* 2015) and may be a good aid to cancer therapy. Active cancer patients often fall at risk of thrombotic complications varying from arterial or venous thromboembolism to disseminated intravascular coagulation and consequential death of cancer patients (Levi, 2014). Anti-coagulants and anti-platelet agents which are nature-derived be incorporated to combat clinical issues in relation to cancer cases. Piperine and pellitorine have the capacity to retard the process of blood coagulation (Ku *et al.,* 2013; Son *et al.,* 2014) and could offer effective support to regular cancer therapy.

Conclusion

Research works conducted till date on *Piper nigrum* L. have showed presence of array of important biomolecules. These scientific evidences provide support to the traditional utilization of this medicinal plant since times immemorial. Again, the biomolecules that are inherent in the plant holds potential to combat human disorders including that of cancer. Piperine, pellitorine and piperidine are three such important biomolecules that are capable of hindering tumor formation, development and metastasis. Piperine can regulate genes at the level of transcription and translation and can halt cell cycle. Piperine is found capable of binding specifically to prooncogenes and regulate them. *In vivo* and *in vitro* studies have confirmed that piperine, pellitorine and piperidine are cytotoxic against cancer cells and initiate cascades that can cause apoptosis of cancer cells. Piperine has been proved to be more versatile and can counter cancer cases even in advanced stages. Piperine can block cancer cell migration and metastasis development and can deal with acquired drug resistances developed during cancer chemotherapy and also act as bioenhancer. Piperine and pellitorine and possibly piperidine are equally important in dealing with clinical issues that develop during tumor development and may therefore complement regular chemotherapy and radiotherapy. They are helpful in situations like inflammation due to tumor formation and blood coagulation in cancer cases.

In the present study, focus was made for a systematic review of data on traditional uses and the phytconstituents present, particularly those having antitumor attributes. These phytochemicals from *Piper nigrum* has been tested on important cancer cell lines that act via different mechanisms of action. Nevertheless, *Piper nigrum* is a great reservoir of anticancer chemical entities. In the search for newer drugs against cancer, *Piper nigrum* seems greatly prospective that may be more effective than the existing ones and expected to be safer for its plant origin. Also, *Piper nigrum* may offer synergistic help to other anticancer molecules or be a support to other approach to cancer therapy.

We here conclude that, *Piper nigrum* proved to be a potent medicinal plant and phytochemicals from this taxon may be useful for development of anticancer drugs. Further, extensive investigation on toxicities, proper standardization and clinical trials may yield effective cancer fighting molecules from this spice taxon that could be markedly gainful for mankind.

Acknowledgement

The authors express deep gratitude to the faculty members of University of Science and Technology, Meghalaya and thankful to the faculty of Gauhati University, Guwahati for the enthusiastic support all throughout.

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Cite this article as:

Chowdhury U* and Baruah P. K. A review on Traditional usage, Phytochemistry, Anticancer molecules of *Piper nigrum* L. (Indian Pepper). *Annals of Plant Sciences.* 10.4. (2021) pp. 4180-4194.

DOI: http://dx.doi.org/10.21746/aps.2021.10.4.1

Subject Editor : Dr. Shaik Mannur Ismail, University Malaysia Terraganu, Malaysia.

Source of support: Nil; **Conflict of interest:** Nil.