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BIOENHANCER: AN AGENT FOR INCREASING BIOAVAILABILITY

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ABSTRACT

Bioenhancer are an agent which are not medicinal individuals however while they combine with an effective pharmaceutical drug start to the increase of the pharmacologic response of the drug. When every drug molecule are being introduced every year but many of these molecules have problems like their solubility, stability, bioavailability and long-lasting side effects. Low bioavailability is one of the serious but treatable problems in the case of the drug molecule. There are also some other circumstances that are obliged for low bioavailability such as low aqueous solubility or effluence by P-gp, etc. These review aims is to discuss the idea of bioavailability to execute a better therapeutic response in suitable dose using natural drugs and natural products like ginger, caraway, aloe, quercetin, glycyrrhizin piperine, curcumin, etc. The use of natural products is for the amount and existent of the drug at which the drug is absorbed improvement because these are harm-free, non-toxic, inexpensive, easily procured, non-addictive, pharmacologically inert and non-allergenic nature, etc. Bioenhancers are utilized for numerous classes of drug-like neutraceuticals, antibiotics, antitubercular and anticancer for instant accouterments. Bioenhancers are also used in several novel drug delivery compositions such as Liposomes, transferosomes, ethosomes, nanoparticles, etc. This review gives the origin of Bioenhancers from natural authorities such as plants and animals with their mechanism and importance in formulation with its future prospective.

KEYWORDS: Bioenhancers, Bioavailability, Piperine, Quercetin.

1. INTRODUCTION

1.1 Definition

Bioenhancers are those substances which increases the bioavailability as well as the bio efficacy of active pharmaceutical substances when they are combined with them without having activity of their own at the dose used.[1]

1.2 Need for bioenhancers

Lipophilicity and size of molecule are the chief preventive factors for molecules to pass the biological membrane and to be immersed systematically following administration through oral or topical route.[2] Some plant extracts and phyto-constituents, regardless of having excellent bioactivity in vitro describes less or no in vivo actions because of their poor lipid solubility or inappropriate size of molecule or both, after that the outcome was reduced absorption and poor bioavailability.[3] Bioenhancers are phyto-molecules which at lower doses nurture and supplement the biological activity of the drug. There are various synthetic and herbal drugs which suffer from the problem of bioavailability.[4] As bioavailability is necessary because it is the rate and extent of a substance to which it enters total systematic circulation and thus available at the required site of action.[5] They are also preferred for such classes of drugs which are poorly efficacious, required prolonged therapy and which are highly toxic and expensive.[6]

When bioenhancers are used in combination with various classes of drugs such as antibiotics, anti-tuberculosis, antiviral, antifungal and anticancer drugs they are seen to be very effective. Bioenhancers act through several mechanisms which may affect mainly absorption process, drug metabolism or action on drug targeting.[7]

1.3 Novel property of bioenhancer

Bioenhancers have different propertieswhich are required for the improvement of bioavailability of drug such as.[8-13]

i. Nontoxic to humans or animal
ii. Should be effective at a very low concentration in a combination
iii. Should be easy to formulate
iv. Enhance uptake or absorption
v. Enhance activity of drug molecule

1.4 Bioavalibilty and Bioefficancy enhancing activity

The term bioavailability or bioenhancing activity is defined as "a substance at a lower dosage level, which in combination with a drug or nutrient provides more availability of the drug by reducing the consumption of the drug or nutrient resulting in enhanced efficacy of the drugs.[14]

The great interests for the improvement of bioavailability of a large number of drugs are poorly available, administered for long periods, toxic, and expensive.[15] Maximizing bioavailability is therapeutically important because the extent of bioavailability directly influences plasma concentrations and consequently therapeutic efficacy. Bioavailability enhancement can make the expensive drugs affordable and reduce the toxic effects by reducing the required dose of drugs.[16]

Poorly bioavailable drugs remain sub-therapeutic because a major portion of a dose never reaches the plasma or exerts its pharmacological effect unless and until very large doses are given which may lead to serious side effects.[17] Any significant improvement in bioavailability will result in lowering the dose or the dose frequency of that particular drug. Intersubject variability is particularly of concern for a drug with a narrow safety margin.[18] Incomplete oral bioavailability includes poor dissolution or low aqueous solubility, poor intestinal membrane permeation, degradation of the drug in gastric or intestinal fluids, and presystemic intestinal or hepatic metabolism.[19] Many therapeutic treatments are also accompanied by loss of essential nutraceuticals in the course of therapy. The bioenhancers improve nutritional status by increasing bioavailability/bioefficacy of various nutraceuticals including metals and vitamins.[20]

1.5 Bioavailability enhancement can be done by the following

(a) Promoting the absorption of the drugs from GIT.[21]

(b) Inhibiting or reducing the rate of biotransformation of drugs in the liver or intestines.[22]

(c) Modifying the immune system in such a way that the overall requirement of the drug is reduced substantially.[23]

(d) Increasing the penetration or the entry into the pathogens even where they become persistors within the macrophages such as for *Mycobacterium tuberculosis* and such others. This eventually ensures the enhanced killing of these organisms is well secured within the places otherwise inaccessible to the active drug.[24]

(e) Inhibiting the capability of pathogens or abnormal tissue to reject the drug, for example, efflux mechanisms frequently encountered with antimalarial, anticancer and antimicrobial drugs.[25]

(f) Modifying the signaling process between host and pathogen ensuring increased accessibility of the drugs to the pathogens.[26]

(g) Enhancing the binding of the drug with the target sites such as receptors, proteins, DNA, RNA, and the like in the pathogen, thus potentiating and prolonging its effect leading to enhanced antibiotic activity against pathogens.[27]

(h) Besides above mode of action, the bioenhancer agents may also be useful for promoting the transport of nutrients and the drugs across the blood brain barrier, which could be of immense help in the control of diseases like cerebral infections, epilepsy, and other CNS problems.[28]

1.6 Mechanisms of action

Herbal bioenhancers act through several mechanisms of action. Different herbal bioenhancers may have same or different mechanisms of action.[29] They increase bioavailability of nutraceuticals by acting on gastrointestinal tract to enhance absorption, whereas they increase bioavailability of drugs by acting on drug metabolism process.[30]

Table: 1.1: Mechanism of Action.

S.No.	Mechanism of Action
1.	Bioenergetic properties[31]
2.	Increases gastrointestinal blood supply and reduces hydrochloric acid secretion[32]
3.	Stimulation of γ-glutamyltranspeptidase (GGT) activity which enhances uptake of amino acids[33]
4.	Cholagogues effect[34]
5.	Thermogenic and bioenergetics properties[35]
6.	Inhibition of gastric emptying time, gastrointestinal transit[36]
7.	Inhibition of drug metabolizing enzymes and suppression of first pass metabolism[37]
8.	Modifications in GIT epithelial cell membrane permeability[38]

2. Herbal bioenhancers

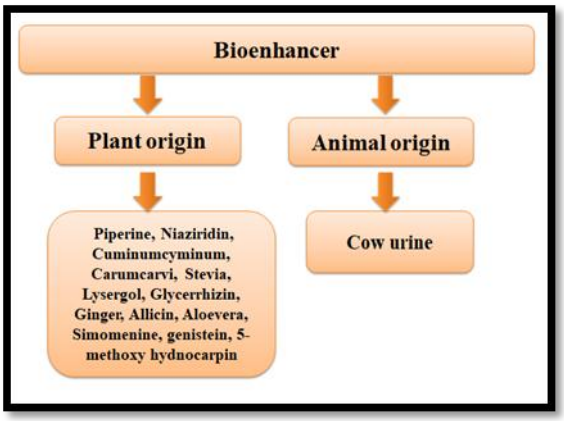

Fig: 1: Classification of Bioenhancer according to their origin.

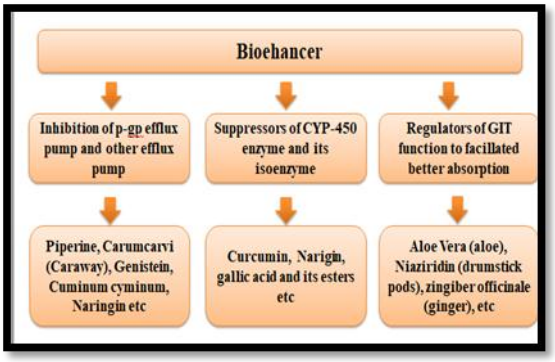

Fig 2: Classification of bioenhancer according to their action.

2.1 Piperine

Piperine, the major plant alkaloid present in *P. nigrum* Linn (Black pepper) and *P. longum* Linn (Long pepper), has bioavailability enhancing activity for some nutritional substances and for some drugs. It has been used extensively as a condiment and flavoring for all types of savory dishes.[39] Piper species have been used in folklore medicine for the treatment of various diseases, including seizure disorders. Piperine is known to exhibit a variety of biological activities which include anti-inflammatory activity, antipyretic activity, fertility enhancement, antifungal activity, antidiarrhoeal activity, antioxidant activity, antimetastatic activity, antithyroid activity, antimutagenic activity, antitumor activity, antidepressant activity, antiplatelet activity, analgesic activity, hepatoprotective activity, antihypertensive activity, and antiasthmatic activity. Piperine exhibits a toxic effect against hepatocytes and cultured hippocampal neurons, reproductive toxicity in swiss albino mice, and immunotoxicity.[40]

Fig 3: Piperine.

2.2 Zingiberofficinale

The major pungent compounds in *Zingiberofficinale* (Ginger) of rhizome extract contain potentially active gingerols, which can be converted to shogaols, zingerone, and paradol. The odor of ginger depends mainly on its volatile oil.[41], the yield of which varies from 1 to 3%. In laboratory animals, the gingerols increase the motility of the gastrointestinal tract and have analgesic, sedative, antipyretic, and antibacterial properties. Gingerol is the major pungent principle of ginger.[42] The chemopreventive potentials of -gingerol present a promising future alternative to expensive and toxic therapeutic agents. Ginger exhibits activities like antiulcer activity, antithrombotic activity, antimicrobial activity, antifungal activity, anti-inflammatory activity, antidiabetic activity, antiemetic activity, anthelmintic activity, analgesic and antipyretic activity, antioxidant and antiapoptotic activity, and anticancer activity Ginger acts powerfully on GIT mucous membrane.[43] The role of ginger is to regulate intestinal function to facilitate absorption. The composition containing *Z. officinale* alone provides bioavailability/bioenhancing activity in the range of 30–75%, and piperine and *Z. officinale*, and provides the bioavailability of drugs.[44] in the range of 10–85%. The dosage of bioenhancer from *Z. officinale* as extract is in the range of 10–30 mg/kg body weight and piperine is in the range of 4–12 mg/kg body weight. The dosage of bioenhancer from *Z. officinale* as bioactive fraction is in the range of 5–15 mg/kg body weight, preferably 30 mg/kg body weight and piperine is in the range of 6–10 mg/kg body weight, preferably 8 mg/kg body weight.[45] The extracts or its fractions either in presence or absence of piperine have been found to be highly selective in their bioavailability enhancing activity. It varies[46] from almost nearly significant (20%) to highly significant (200%).

Fig: 4: Gingerol.

2.3 Niaziridin

Niaziridin is a nitrile glycoside that has been isolated from the leaves, pods, and bark of Drumstick (*Moringaoleifera*). *M. oleifera* has shown to exhibit activities like antifertility effect, antimicrobial activity, diuretic activity, anticancer activity, anti-inflammatory activity, hypotensive and spasmolytic activity, antifungal activity, antiulcer activity, antioxidant activity, hepatoprotective activity, hypolipidaemic activity, antiteratogenic activity, and antiarthritic activity.[47]

It enhances bioactivity of commonly used antibiotics such as rifampicin, ampicillin, tetracycline, and nalidixic acid against Gram-positive bacteria like *M. smegmatis* and *Bacillus subtilis* and Gram-negative bacteria[47] like *E. coli*. It enhances activity of commonly used antibiotics such as rifampicin, ampicillin, tetracycline, and nalidixic acids against *E. coli* Gram-negative bacteria. It enhances activity of rifampicin, ampicillin, tetracycline, and nalidixic acids by 1.2–19-fold against the Gram-positive strains.[48] It enhances the activity of azole antifungal drugs such as clotrimazole against *Candida albicans* by 5-6-fold. However, the antifungal activity enhancement was observed only at a relatively higher concentration (10 g/mL) of the compound.[49] It also facilitates the uptake of nutrients like Vitamin B_{12} through the intestinal gut membrane in combination, thus also functioning as bioavailability enhancer.[50]

Fig: 5: Niaziridin.

2.4 Glycyrrhizin

Glycyrrhizin is a glycoside obtained from roots and stolon of Liquorice (*Glycyrrhizaglabra*). It has expectorant action to treat bronchitis and can also reduce inflammation, allergies, asthma, gastritis, peptic ulcers, rheumatism, and sore throat.[51] It helps the liver to detoxify drugs and is used for treatment of liver disease. It strengthens the immune system, stimulates the adrenal gland, and is diuretic and laxative. Glycyrrhizin is 50 times sweeter than sugar. Primary uses include treatment for peptic ulcers and stomach ailments, respiratory, and intestinal passages.[52] Glycyrrhizin exhibits activities like antihepatotoxic activity, anti-inflammatory activity, anticancer activity, and antiviral activity.[53] The concentration of glycyrrhizin ranges from 0.05 to 50% of the weight of the antibacterial compounds. The concentration of glycyrrhizin ranges from 0.10 to 10% of the weight of the nutraceutical compounds.[54] The concentration of glycyrrhizin ranges from 0.25 to 20% of the weight of the antifungal agents. The level of glycyrrhizin ranges from 10 to 10,000-fold of the weight of the anticancer compound used.[55]

Glycyrrhizin-mediated enhancement in the cell division inhibitory action of anticancer agent "Taxol" (paclitaxel) in the animal cell culture experiments[56] using cancerous cell line MCF-7. The anticancerous activity of Taxol in terms of inhibiting the growth and multiplication of MCF-7 cancer cells was markedly enhanced by 5-fold. The cancerous cells growth inhibition by Taxol (0.01 g/mL) in presence of glycyrrhizin (1 g/mL) was higher than even the treatment with Taxol (0.05 g/mL) alone.[57]

Fig 6: Glycyrrhizin plant.

2.5 CuminumCyminum

The main components of *C. cyminum* oil are *p*-mentha-1,4-dien-7-al, cumin aldehyde, *γ*-terpinene, and *β*-pinene. *C. cyminum* exhibits activities like estrogenic activity, hypolipidaemic activity, antinociceptive and anti-inflammatory activity, anticonvulsant effect, anticancer activity, antimicrobial activity, antitussive effect, antioxidant activity, and antifungal activity.[58] The doses of its fractions responsible for the bioavailability enhancement activity ranged from 0.5 to 25 mg/kg body weight. The dosage level of the composition comprising *C. cyminum* extract is in the range of 10–30 mg/kg body weight and composition comprising bioactive fraction is in the range of 2–20 mg/kg body weight. The composition of *C. cyminum* extract or the fractions there of which provides bioavailability/bioenhancing activity[59] in the range of 25–335%.

Fig 7: Cuminum Cyminum plant.

2.6 Stevia Rebaudiana

Stevia rebaudiana (Stevia) is known as honey leaf which has been used as sweetener in South America. The chief constituent of stevia is stevioside, the glycoside which is 200 times sweeter than sucrose.[60] Other constituents include steviol, austroinulin, rebaudioside, and dulcoside A. Extracts/fractions/pure isolates of stevia either alone or in combination with piperine are selective in enhancing the bioavailability/bioefficacy of drugs, nutraceuticals, and herbal drugs/formulations.[61] The percentage of stevia in the bioenhancing composition varies from 0.01 to 80%. The dosage of bioenhancer derived from stevia extract is in the range of 0.01–50 mg/kg body weight and piperine is in the range of 0.01–12 mg/kg body weight.[62] The dosage of bioenhancer derived from stevia bioactive fraction or pure compound is in the range of 0.01–40 mg/kg body weight, preferably 30 mg/kg body weight and piperine is in the range of 0.01–10 mg/kg body weight, preferably 8 mg/kg body weight.[63] The dosage of bioenhancer derived from stevia leaf is in the range of 0.01–250 mg/dose of the drug, nutraceutical, or herbal extract. The dosage of bioenhancer derived

from stevia fraction or pure compound is in the range of 0.01–75 mg irrespective of the amount of drug in the composition, preferably 1–30 mg/dose of the drug, nutraceutical, or herbal extract. Stevia enhanced bioavailability of different groups like antibiotics, antiobese drugs, antidiabetic drugs, antifungal drugs, antiviral drugs, anticancer drugs, cardiovascular drugs, anti-inflammatory, antiarthritic agents, antituberculosis/antileprosy drugs, anthelmintic/respiratory drugs, immune-modulators, antiulcer drugs, and herbal products or drugs.[64]

Fig 8: Stevia Rebudiana.

2.7 Curcumin

Curcumin is the principal curcuminoid of the popular Indian spice turmeric (*Curcuma longa*). Curcumin suppresses drug metabolizing enzymes (CYP3A4) in the liver as well as inducing changes in the drug transporter P-glycoprotein, hence increasing the Cmax and AUC of celiprolol and midazolam in rats.[65] The influence of curcumin before treatment on pharmacokinetic disposition of norfloxacin was studied in rabbits after single oral administration. The pharmacokinetic data revealed that curcumin-treated animals had significantly higher AUC and AUMC.[66]

Fig 9: Curcumin plant.

2.8 Quercetin

Quercetin is a plant-derived flavonoid found in fruits, vegetables, leaves, and grains.[67] Quercetin has exhibited activities including antioxidant, radical scavenging, anti-inflammatory, antiatherosclerotic, anticancer, and antiviral effects.[68] Quercetin is an inhibitor of CYP3A4 and a modulator of P-glycoprotein. It has been shown to decrease bioavailability of cyclosporin in pigs and rats.[69-70]

Fig 10: Quercetin.

2.9 Naringin

Naringin is the major flavonoid glycoside found in grapefruit, apples, onions, and tea.[71-72] Naringin exerts a variety of pharmacological effects such as antioxidant activity, antiulcer activity, antiallergic activity and anticancer activity, and blood lipid lowering. Naringin has been reported as a CYP3A4 inhibitor as well as a P-glycoprotein modulator.[73]

Fig 11: Naringin.

2.10 Cow urine distillate

Cow urine distillate is more effective as bioenhancer than cow urine, to increase the effectiveness of antimicrobial, antifungal, and anticancer drugs.[74]

Cow urine has antitoxic activity against the cadmium chloride toxicity and it can be used as a bioenhancer of zinc.[75-77] Mature male mice exposed to cadmium chloride only showed 0% fertility rate.[78] However, the animals exposed to cadmium chloride + cow urine distillate + zinc sulfate showed 90% fertility rate with 100% viability and lactation indices.[79-80] Fertility index was also found to be 88% in group treated with cadmium chloride + cow urine distillate.[81-82] Thus, these results indicate that cow urine distillate works as an antitoxic against the cadmium chloride toxicity and it can be used as a bioenhancer of zinc.[83] Cow urine distillate increased the activity of rifampicin by about 5–7 times against *Escherichia coli* and 3–11 times against Gram-positive bacteria.[84-85] It probably acts by enhancing the transport of antibiotics across the membrane of gastrointestinal tract. The enhancement in transport is approximately 2–7 times.[86-89]

3. CONCLUSIONS

The effective formulation strategy for the optimization of the pharmacokinetic characteristics of dietary components is crucial to improve their *in vivo* performance and ultimately maximize their effectiveness as a bioavailability enhancer.[90-91] The available scientific research on bioenhancers has shown to produce significant enhancing effect on bioavailability when coadministered or pretreated with many drugs and nutraceuticals.[92-94] These natural compounds include piperine, *Zingiberofficinale*, niaziridin, glycyrrhizin, *Cuminumcyminum*, *Carumcarvi*, allicin, lysergol, *Aloe vera*, *Stevia rebaudiana*, curcumin, sinomenine, genistein, *Ammanniamultiflora*, capsaicin, quercetin, naringin, capmul and cow urine distillate.[95-96] They reduce the dose, shorten treatment, and thus reduce drug-resistance and drug toxicity or adverse reactions.[97-99] Due to dose economy, treatment is cost-effective. Bioenhancers are also found to decrease or having no effect or little effect on the bioavailability of some drugs.[100-104]

The current paper discussed the enhancing effects of bioenhancers of drugs in animals and humans but these compounds have not been completely explored in experimental animals till date. However, these studies lack information on their exact mechanism of action, toxicity evaluation of extracts, and suitable combinations. Therefore, we have to focus on this area for further research on their active principles, mechanisms of actions, toxicity evaluation, and suitable combinations with other drugs. So we can explore novel principles with high bioenhancing ability and less toxic effects.

REFERENCES

1. N. Atal and K. L. Bedi, "Bioenhancers: revolutionary concept to market," *Journal of Ayurveda and Integrative Medicine*, 2010; 1(2): 96–99.
2. S. P. S. Khanuja, J. S. Arya, S. K. Srivastava et al., "Antibiotic pharmaceutical composition with lysergol as bioenhancer and method of treatment," United States Patent Number, 20070060604A1, 2007.
3. G. N. Qazi, K. L. Bedi, R. K. Johri et al., "Bioavailability enhancing activity of *Carumcarvi* extracts and fractions thereof," United States Patent Number, US20070020347A1, 2007.
4. P. Breedveld, J. H. Beijnen, and J. H. M. Schellens, "Use of P-glycoprotein and BCRP inhibitors to improve oral bioavailability and CNS penetration of anticancer drugs," *Trends in Pharmacological Sciences*, 2006; 27(1): 17–24.
5. M. J. Kang, J. Y. Cho, B. H. Shim, D. K. Kim, and J. Lee, "Bioavailability enhancing activities of natural compounds from medicinal plants," *Journal of Medicinal Plant Research*, 2009; 3(13): 1204–1211.
6. I. A. Khan, Z. M. Mirza, A. Kumar, V. Verma, and G. N. Qazi, "Piperine, a phytochemical potentiator of ciprofloxacin against Staphylococcus aureus," *Antimicrobial Agents and Chemotherapy*, 2006; 50(2): 810–812.
7. S. Bajad, K. L. Bedi, A. K. Singla, and R. K. Johri, "Piperine inhibits gastric emptying and gastrointestinal transit in rats and mice," *Planta Medica*, 2001; 67(2): 176–179.
8. R. K. Bhardwaj, H. Glaeser, L. Becquemont, U. Klotz, S. K. Gupta, and M. F. Fromm, "Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4," *Journal of Pharmacology and Experimental Therapeutics*, 2002; 302(2): 645–650.
9. A. Khajuria, N. Thusu, and U. Zutshi, "Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics," *Phytomedicine*, 2002; 9(3): 224–231.
10. S. Kumar, V. Singhal, R. Roshan, A. Sharma, G. W. Rembhotkar, and B. Ghosh, "Piperine inhibits TNF-α induced adhesion of neutrophils to endothelial monolayer through suppression of NF-κB and IκB kinase activation," *European Journal of Pharmacology*, 2007; 575: 1–3, 177–186.

11. K. A. Naidu and N. B. Thippeswamy, "Inhibition of human low density lipoprotein oxidation by active principles from spices," *Molecular and Cellular Biochemistry*, 2002; 229: 1-2 19–23.
12. R. S. Vijayakumar, D. Surya, and N. Nalini, "Antioxidant efficacy of black pepper (*Piper nigrum* L.) and piperine in rats with high fat diet induced oxidative stress," *Redox Report*, 2004; 9(2): 105–110.
13. I. Gülçin, "The antioxidant and radical scavenging activities of black pepper (*Piper nigrum*) seeds," *International Journal of Food Sciences and Nutrition*, 2005; 56(7): 491–499.
14. K. Selvendiran, R. Padmavathi, V. Magesh, and D. Sakthisekaran, "Preliminary study on inhibition of genotoxicity by piperine in mice," *Fitoterapia*, 2005; 76: 3-4 296–300.
15. N. Jain and R. N. Mishra, "Antioxidant activity of TrikatumegaExt," *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2011; 2: 624–624.
16. C. R. Pradeep and G. Kuttan, "Effect of piperine on the inhibition of lung metastasis induced B16F-10 melanoma cells in mice," *Clinical and Experimental Metastasis*, 2002; 19(8): 703–708.
17. S. Panda and A. Kar, "Piperine lowers the serum concentrations of thyroid hormones, glucose and hepatic 5′D activity in adult male mice," *Hormone and Metabolic Research*, 2003; 35(9): 523–526.
18. R. S. Vijayakumar and N. Nalini, "Piperine, an active principle from *Piper nigrum*, modulates hormonal and apolipoprotein profiles in hyperlipidemic rats," *Journal of Basic and Clinical Physiology and Pharmacology*, 2006; 17(2): 71–86.
19. R. El Hamss, M. Idaomar, A. Alonso-Moraga, and A. Muñoz Serrano, "Antimutagenic properties of bell and black peppers," *Food and Chemical Toxicology*, 2003; 41(1): 41–47.
20. K. Selvendiran, S. M. Banu, and D. Sakthisekaran, "Oral supplementation of piperine leads to altered phase II enzymes and reduced DNA damage and DNA-protein cross links in Benzo(a)pyrene induced experimental lung carcinogenesis," *Molecular and Cellular Biochemistry*, 2005; 268: 1-2 141–147.
21. K. Srinivasan, "Black pepper and its pungent principle-piperine: a review of diverse physiological effects," *Critical Reviews in Food Science and Nutrition*, 2007; 47(8): 735–748.

22. S. Wongpa, L. Himakoun, S. Soontornchai, and P. Temcharoen, "Antimutagenic effects of piperine on cyclophosphamide-induced chromosome aberrations in rat bone marrow cells," *Asian Pacific Journal of Cancer Prevention*, 2007; 8(4): 623–627.
23. E. S. Sunila and G. Kuttan, "Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine," *Journal of Ethnopharmacology*, 2004; 90: 2-3 339–346.
24. S. Manoharan, S. Balakrishnan, V. P. Menon, L. M. Alias, and A. R. Reena, "Chemopreventive & efficacy of curcumin and piperine during 7,12-dimethylbenz (a)anthracene-induced hamster buccal pouch carcinogenesis," *Singapore Medical Journal*, 2009; 50(2): 139–146.
25. S. A. Lee, S. S. Hong, X. H. Han et al., "Piperine from the fruits of *Piper longum* with inhibitory effect on monoamine oxidase and antidepressant-like activity," *Chemical and Pharmaceutical Bulletin*, 2005; 53(7): 832–835.
26. S. Li, C. Wang, M. Wang, W. Li, K. Matsumoto, and Y. Tang, "Antidepressant like effects of piperine in chronic mild stress treated mice and its possible mechanisms," *Life Sciences*, 2007; 80(15): 1373–1381.
27. J. Wattanathorn, P. Chonpathompikunlert, S. Muchimapura, A. Priprem, and O. Tankamnerdthai, "Piperine, the potential functional food for mood and cognitive disorders," *Food and Chemical Toxicology*, 2008; 46(9): 3106–3110.
28. B. S. Park, D. J. Son, Y. H. Park, T. W. Kim, and S. E. Lee, "Antiplatelet effects of acidamides isolated from the fruits of *Piper longum* L," *Phytomedicine*, 2007; 14(12): 853–855.
29. S. Pooja, R. P. Agrawal, P. Nyati, V. Savita, and P. Phadnis, "Analgesic activity of*Pipernigrum*extract per se and its interaction with diclofenac sodium and pentazocine in albino mice," *The Internet Journal of Pharmacology*, 2007; 5(1): 3.
30. H. Matsuda, K. Ninomiya, T. Morikawa, D. Yasuda, I. Yamaguchi, and M. Yoshikawa, "Protective effects of amide constituents from the fruit of Piper chaba on d-galactosamine/TNF-α-induced cell death in mouse hepatocytes," *Bioorganic and Medicinal Chemistry Letters*, 2008; 18(6): 2038–2042.
31. S. I. H. Taqvi, A. J. Shah, and A. H. Gilani, "Blood pressure lowering and vasomodulator effects of piperine," *Journal of Cardiovascular Pharmacology*, 2008; 52(5): 452–458.
32. S. H. Kim and Y. C. Lee, "Piperine inhibits eosinophil infiltration and airway hyperresponsiveness by suppressing T cell activity and Th2 cytokine production in the ovalbumin-induced asthma model," *Journal of Pharmacy and Pharmacology*, 2009; 61(3): 353–359.

33. R. K. S. Dogra, S. Khanna, and R. Shanker, "Immunotoxicological effects of piperine in mice," *Toxicology*, 2004; 196(3): 229–236.
34. K. Selvendiran, S. M. Banu, and D. Sakthisekaran, "Protective effect of piperine on benzo(a)pyrene-induced lung carcinogenesis in *Swiss albino* mice," *Clinica Chimica Acta*, 2004; 350: 1-2 73–78.
35. K. Selvendiran, J. P. V. Singh, K. B. Krishnan, and D. Sakthisekaran, "Cytoprotective effect of piperine against benzo[a]pyrene induced lung cancer with reference to lipid peroxidation and antioxidant system in Swiss albino mice," *Fitoterapia*, 2003; 74: 1-2 109–115.
36. K. Selvendiran, P. Senthilnathan, V. Magesh, and D. Sakthisekaran, "Modulatory effect of Piperine on mitochondrial antioxidant system in Benzo(a)pyrene-induced experimental lung carcinogenesis," *Phytomedicine*, 2004; 11(1): 85–89.
37. K. Selvendiran, C. Thirunavukkarasu, J. P. V. Singh, R. Padmavathi, and D. Sakthisekaran, "Chemopreventive effect of piperine on mitochondrial TCA cycle and phase-I and glutathione-metabolizing enzymes in benzo(a)pyrene induced lung carcinogenesis in Swiss albino mice," *Molecular and Cellular Biochemistry*, 2005; 271: 1-2 101–106.
38. B. M. Choi, S. M. Kim, T. K. Park et al., "Piperine protects cisplatin-induced apoptosis via heme oxygenase-1 induction in auditory cells," *Journal of Nutritional Biochemistry*, 2007; 18(9): 615–622.
39. J. Q. Zhao, G. Z. Du, Y. C. Xiong, Y. F. Wen, M. Bhadauria, and S. K. Nirala, "Attenuation of beryllium induced hepatorenal dysfunction and oxidative stress in rodents by combined effect of gallic acid and piperine," *Archives of Pharmacal Research*, 2007; 30(12): 1575–1583.
40. N. Pathak and S. Khandelwal, "Comparative efficacy of piperine, curcumin and picroliv against Cd immunotoxicity in mice," *BioMetals*, 2008; 21(6): 649–661.
41. L. G. Lala, P. M. D'Mello, and S. R. Naik, "Pharmacokinetic and pharmacodynamic studies on interaction of "trikatu" with diclofenac sodium," *Journal of Ethnopharmacology*, 2004; 91: 2-3 277–280.
42. J. Shaikh, D. D. Ankola, V. Beniwal, D. Singh, and M. N. V. R. Kumar, "Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer," *European Journal of Pharmaceutical Sciences*, 2009; 37: 3-4 223–230.

43. D. Suresh and K. Srinivasan, "Tissue distribution & elimination of capsaicin, piperine &curcumin following oral intake in rats," *Indian Journal of Medical Research*, 2010; 131(5): 682–691.
44. S. Pattanaik, D. Hota, S. Prabhakar, P. Kharbanda, and P. Pandhi, "Effect of piperine on the steady-state pharmacokinetics of phenytoin in patients with epilepsy," *Phytotherapy Research*, 2006; 20(8): 683–686.
45. V. Balakrishnan, S. Varma, and D. Chatterji, "Piperine augments transcription inhibitory activity of rifampicin by severalfold in *Mycobacterium smegmatis*," *Current Science*, 2001; 80(10): 1302–1305.
46. A. R. Hiwale, J. N. Dhuley, and S. R. Naik, "Effect of co-administration of piperine on pharmacokinetics of *β*-lactam antibiotics in rats," *Indian Journal of Experimental Biology*, 2002; 40(3): 277–281.
47. J. D. Lambert, J. Hong, D. H. Kim, V. M. Mishin, and C. S. Yang, "Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice," *Journal of Nutrition*, 2004; 134(8): 1948–1952.
48. M. Singh, C. Varshneya, R. S. Telang, and A. K. Srivastava, "Alteration of pharmacokinetics of oxytetracycline following oral administration of *Piper longum* in hens," *Journal of Veterinary Science*, 2005; 6(3): 197–200.
49. B. S. Balkrishna and P. V. Yogesh, "Influence of co-administration of piperine on pharmacokinetic profile of ciprofloxacin," *Indian Drugs*, 2002; 39(3): 166–168.
50. R. Kasibhatta and M. U. R. Naidu, "Influence of piperine on the pharmacokinetics of nevirapine under fasting conditions: a randomised, crossover, placebo-controlled study," *Drugs in R and D*, 2007; 8(6): 383–391.
51. M. S. Dama, C. Varshneya, M. S. Dardi, and V. C. Katoch, "Effect of trikatupretreatment on the pharmacokinetics of pefloxacin administered orally in mountain Gaddi goats," *Journal of Veterinary Science*, 2008; 9(1): 25–29.
52. K. Janakiraman and R. Manavalan, "Compatibility and stability studies of ampicillin trihydrate and piperine mixture," *International Journal of Pharmaceutical Sciences and Research*, 2008; 2: 1176–1181.
53. S. Pattanaik, D. Hota, S. Prabhakar, P. Kharbanda, and P. Pandhi, "Pharmacokinetic interaction of single dose of piperine with steady-state carbamazepine in epilepsy patients," *Phytotherapy Research*, 2009; 23(9): 1281–1286.

54. M. J. Jin and H. K. Han, "Effect of piperine, a major component of black pepper, on the intestinal absorption of fexofenadine and its implication on food-drug interaction," *Journal of Food Science*, 2010; 75(3): H93–H96.
55. A. Singh, V. K. Pawar, V. Jakhmola, M. H. Parabia, R. Awasthi, and G. Sharma, "*In vivo* assessment of enhanced bioavailability of metronidazole with piperine in rabbits," *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 2010; 1(4): 273–278.
56. K. Janakiraman and R. Manavalan, "Studies on effect of piperine on oral bioavailability of ampicillin and norfloxacin," *African Journal of Traditional, Complementary and Alternative Medicines*, 2011; 5: 257–262.
57. J. J. Johnson, M. Nihal, I. A. Siddiqui et al., "Enhancing the bioavailability of resveratrol by combining it with piperine," *Molecular Nutrition and Food Research*, 2011; 55(8): 1169–1176.
58. S. Patel, S. Devada, H. Patel, N. Patel, S. Bhavsar, and A. Thaker, "Influence of co-administration of piperine on pharmacokinetic profile of gatifloxacin in layer birds," *Global Veterinaria*, 2011; 7: 427–432.
59. S. S. Devada, S. D. Patel, H. B. Patel, N. N. Patel, S. K. Bhavsar, and A. M. Thaker, "Bioenhancing activity of piperine on pharmacokinetics of gatifloxacin in broiler birds," Inventi Impact: PlantaActiva, 2011, Article ID: Inventi:ppa/10/11, 2011, http://www.inventi.in/Article/ppa/10/11.aspx.
60. A. Singh and S. Chand, "Improved bioavailability of atenolol with piperine in rats," *International Journal of Pharmaceutical Research*, 2011; 3: 88–91.
61. S. Venkatesh, K. D. Durga, Y. Padmavathi, B. M. Reddy, and R. Mullangi, "Influence of piperine on ibuprofen induced antinociception and its pharmacokinetics," *Drug Research*, 2011; 61: 506–509.
62. A. Singh, D. A. Jain, S. Kumar, N. Jaishwal, R. K. Singh, and P. S. Patel, "Enhanced bioavailability of losartan potassium with piperine in rats," *International Journal of Pharmacy Research and Technology*, 2012; 2: 34–36.
63. R. S. Kapil, U. Zutshi, K. L. Bedi et al., "Pharmaceutical compositions containing piperine and an antituberculosis or antileprosy drug," European Patent Number, EP0650728B1, 2002.
64. P. C. Chawla, "Resorine:a novel CSIR drug curtails TB treatment," *CSIR News*, 2010; 60: 52–54.

65. S. D. Jolad, R. C. Lantz, A. M. Solyom, G. J. Chen, R. B. Bates, and B. N. Timmermann, "Fresh organically grown ginger (*Zingiberofficinale*): composition and effects on LPS-induced PGE2 production," *Phytochemistry*, 2004; 65(13): 1937–1954.
66. W. C. Evans, *Ginger. Trease and Evans Pharmacognosy*, WB Saunders, Edinburgh, UK, 15th edition, 2002.
67. A. A. Oyagbemi, A. B. Saba, and O. I. Azeez, "Molecular targets of [6]-gingerol: its potential roles in cancer chemoprevention," *Bio Factors*, 2010; 36(3): 169–178.
68. M. Thomson, K. K. Al-Qattan, S. M. Al-Sawan, M. A. Alnaqeeb, I. Khan, and M. Ali, "The use of ginger (*Zingiberofficinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent," *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2002; 67(6): 475–478.
69. G. C. Jagetia, M. S. Baliga, P. Venkatesh, and J. N. Ulloor, "Influence of ginger rhizome (*Zingiberofficinale* Rosc) on survival, glutathione and lipid peroxidation in mice after whole-body exposure to Gamma radiation," *Radiation Research*, 2003; 160(5): 584–592.
70. C. Ficker, M. L. Smith, K. Akpagana et al., "Bioassay-guided isolation and identification of antifungal compounds from ginger," *Phytotherapy Research*, 2003; 17(8): 897–902.
71. R. Grzanna, L. Lindmark, and C. G. Frondoza, "Ginger-an herbal medicinal product with broad anti-inflammatory actions," *Journal of Medicinal Food*, 2005; 8(2): 125–132.
72. J. A. O. Ojewole, "Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of *Zingiberofficinale* (Roscoe) rhizomes (*Zingiberaceae*) in mice and rats," *Phytotherapy Research*, 2006; 20(9): 764–772.
73. J. K. Kim, Y. Kim, K. M. Na, Y. J. Surh, and T. Y. Kim, "[6]-gingerol prevents UVB-induced ROS production and COX-2 expression *in vitro* and *in vivo*," *Free Radical Research*, 2007; 41(5): 603–614.
74. Z. M. Al-Amin, M. Thomson, K. K. Al-Qattan, and M. Ali, "Anti-diabetic and hypolipidaemic properties of ginger (*Zingiberofficinale*) in streptozotocin-induced diabetic rats," *British Journal of Nutrition*, 2006; 96(4): 660–666.
75. S. A. Boone and K. M. Shields, "Treating pregnancy-related nausea and vomiting with ginger," *Annals of Pharmacotherapy*, 2005; 39(10): 1710–1713.
76. N. Chaiyakunapruk, N. Kitikannakorn, S. Nathisuwan, K. Leeprakobboon, and C. Leelasettagool, "The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis," *American Journal of Obstetrics and Gynecology*, 2006; 194(1): 95–99.

77. Z. Iqbal, M. Lateef, M. S. Akhtar, M. N. Ghayur, and A. H. Gilani, "In vivo anthelmintic activity of ginger against gastrointestinal nematodes of sheep," *Journal of Ethnopharmacology*, 2006; 106(2) 285–287.
78. Y. Shukla and M. Singh, "Cancer preventive properties of ginger: a brief review," *Food and Chemical Toxicology*, 2007; 45(5): 683–690.
79. G. N. Qazi, K. L. Bedi, R. K. Johri et al., "Bioavailability enhancing activity of *Zingiberofficinale* and its extracts/fractions thereof," United States Patent Number, US2003/0170326A1, 2003.
80. G. N. Qazi, C. L. Tikoo, A. K. Gupta et al., "Bioavailability enhancing activity of *Zingiberofficinale* Linn and its extracts/fractions thereof," World Intellectual Property Organization, International Publication Number, WO03049753A1, 2003.
81. K. Shanker, M. M. Gupta, S. K. Srivastava, D. U. Bawankule, A. Pal, and S. P. S. Khanuja, "Determination of bioactive nitrile glycoside(s) in drumstick (*Moringaoleifera*) by reverse phase HPLC," *Food Chemistry*, 2007; 105(1): 376–382.
82. P. Siddhuraju and K. Becker, "Antioxidant properties of various solvent extracts of total phenolic constituents from three different agroclimatic origins of drumstick tree (*Moringaoleifera* Lam.) leaves," *Journal of Agricultural and Food Chemistry*, 2003; 51(8): 2144–2155.
83. N. Oinam, A. Urooj, P. P. Phillips, and N. P. Niranjan, "Effect of dietary lipids and drumstick leaves (*Moringaoleifera*) on lipid profile and antioxidant parameters in rats," *Food and Nutrition Sciences*, 2012; 3: 141–145.
84. L. Pari and N. A. Kumar, "Hepatoprotective activity of *Moringaoleifera* on antitubercular drug-induced liver damage in rats," *Journal of Medicinal Food*, 2002; 5(3): 171–177.
85. L. K. Mehta, R. Balaraman, A. H. Amin, P. A. Bafna, and O. D. Gulati, "Effect of fruits of *Moringaoleifera* on the lipid profile of normal and hypercholesterolaemic rabbits," *Journal of Ethnopharmacology*, 2003; 86: 2-3 191–195.
86. K. B. Saravillo and A. A. Herrera, "Biological activity of *Moringaoleifera* Lam. (Malunggay) crude seed extract," *Philippine Agricultural Scientist*, 2004; 87(1): 96–100.
87. S. G. Mahajan, R. G. Mali, and A. A. Mehta, "Protective effect of ethanolic extract of seeds of *Moringaoleifera* Lam. against inflammation associated with development of arthritis in rats," *Journal of Immunotoxicology*, 2007; 4(1): 39–47.
88. S. P. S. Khanuja, J. S. Arya, T. Ranganathan et al., "Nitrile glycoside useful as a bioenhancer of drugs and nutrients, process of its isolation from *Moringaoleifera*," United States Patent Number, US006858588B2, 2005.

89. S. P. S. Khanuja, J. S. Arya, T. Ranganathan et al., "Nitrile glycoside useful as a bioenhancer of drugs and nutrients, process of its isolation from Moringaoleifera," European Patent Number, EP1611148B1, 2008.
90. J. M. Crance, N. Scaramozzino, A. Jouan, and D. Garin, "Interferon, ribavirin, 6-azauridine and glycyrrhizin: antiviral compounds active against pathogenic flaviviruses," *Antiviral Research*, 2003; 58(1): 73–79.
91. S. P. S. Khanuja, S. Kumar, J. S. Arya et al., "Composition comprising pharmaceutical/nutraceutical agent and a bioenhancer obtained from Glycyrrhizaglabra," United States Patent Number, US006979471B1, 2005.
92. S. P. S. Khanuja, S. Kumar, J. S. Arya et al., "Composition comprising pharmaceutical/nutraceutical agent and a bioenhancer obtained from Glycyrrhizaglabra," United States Patent Number, US20060057234A1, 2006.
93. N. S. Iacobellis, P. Lo Cantore, F. Capasso, and F. Senatore, "Antibacterial activity of *Cuminumcyminum* L. and *Carumcarvi* L. essential oils," *Journal of Agricultural and Food Chemistry*, 2005; 53(1): 57–61.
94. S. Dhandapani, V. R. Subramanian, S. Rajagopal, and N. Namasivayam, "Hypolipidemic effect of *Cuminumcyminum* L. on alloxan-induced diabetic rats," *Pharmacological Research*, 2002; 46(3): 251–255.
95. M. Sayyah, A. Peirovi, and M. Kamalinejad, "Anti-nociceptive effect of the fruit essential oil of *Cuminumcyminum* L. in rat," *Iranian Biomedical Journal*, 2002; 6(4): 141–145.
96. M. Sayyah, A. Mahboubi, and M. Kamalinejad, "Anticonvulsant effect of the fruit essential oil of *Cuminumcyminum* in mice," *Pharmaceutical Biology*, 2002; 40(6): 478–480.
97. Gagandeep, S. Dhanalakshmi, E. Méndiz, A. R. Rao, and R. K. Kale, "Chemopreventive effects of *Cuminumcyminum* in chemically induced forestomach and uterine cervix tumors in murine model systems," *Nutrition and Cancer*, 2003; 47(2): 171–180.
98. L. Gachkar, D. Yadegari, M. B. Rezaei, M. Taghizadeh, S. A. Astaneh, and I. Rasooli, "Chemical and biological characteristics of *Cuminumcyminum* and *Rosmarinusofficinalis* essential oils," *Food Chemistry*, 2007; 102(3): 898–904.
99. M. H. Boskabady, S. Kiani, H. Azizi, and T. Khatami, "Antitussive effect of *Cuminumcyminum* Linn. in guinea pigs," *Natural Product Radiance*, 2006; 5: 266–269.
100. A. H. El-Ghorab, M. Nauman, F. M. Anjum, S. Hussain, and M. Nadeem, "A Comparative study on chemical composition and antioxidant activity of ginger

(*Zingiberofficinale*) and cumin (*Cuminumcyminum*)," *Journal of Agricultural and Food Chemistry*, 2010; 58(14): 8231–8237.

101. M. B. H. Pai, G. M. Prashant, K. S. Murlikrishna, K. M. Shivakumar, and G. N. Chandu, "Antifungal efficacy of *Punicagranatum*, *Acacia nilotica*, *Cuminumcyminum* and *Foeniculumvulgare* on *Candida albicans*: an *in vitro* study," *Indian Journal of Dental Research*, 2010; 21(3): 334–336.
102. G. N. Qazi, K. L. Bedi, R. K. Johri et al., "Bioavailability/bioefficacy enhancing activity of *Cuminumcyminum* and extracts and fractions thereof," United States Patent Number, US007514105B2, 2009.
103. L. De Martino, V. De Feo, F. Fratianni, and F. Nazzaro, "Chemistry, antioxidant, antibacterial and antifungal activities of volatile oils and their components," *Natural Product Communications*, 2009; 4(12): 1741–1750.
104. S. Lahlou, A. Tahraoui, Z. Israili, and B. Lyoussi, "Diuretic activity of the aqueous extracts of *Carumcarvi* and *Tanacetumvulgare* in normal rats," *Journal of Ethnopharmacology*, 2007; 110(3): 458–463.