Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2017, 9(6):177-184

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Bioavailability Enhancing Agents of Indian Origin

Animisha Mokkapati, Radhakrishna Nagumantri and Satyanarayana Rentala*

Department of Biotechnology, GITAM Institute of Technology, GITAM University, Gandhi Nagar, Visakhapatnam, Andhra Pradesh, India

---

ABSTRACT

Bioavailabilities enhancing agents or bioenhancers are the agents which increase the bioavailability of drugs and nutrients. Many drugs have the issue of low bioavailability. With the usage of bioenhancers it is possible to overcome the drug absorption. Bioenhancers are not effective on their own but when conjugated or co-administered with other drugs, they increase the bioavailability of the drugs. These bioenhancers can reduce the dose, dosage, drug resistance problems and make the treatment cost effective. The mechanism of bioenhancing property of these agents play vital role in pharma industries to decrease the cost of the production of the drugs. In this review, several bioavailability agents of Indian origin are discussed.

Keywords: Bioavailability enhancing agents; p-glycoprotein; Cytochrome p450 enzymes; Drug elimination; Drug absorption

---

INTRODUCTION

Bioavailability is defined as the rate and degree to which a substance enters systemic circulation and available at the site of activity [1]. Bioenhancers are chemical entities that are used to increase the bioavailability of various drugs which are poorly available, harmful, administered for lengthy intervals and expensive. Intravenous administration of drugs achieves maximum bioavailability whereas oral administration of drugs gives low bioavailability [2]. Several therapeutics bear the issue of low bioavailability upon oral administration because of poor absorption and undergo first pass metabolism. The poorly absorbed drugs remain in the physiological system and lead to several adverse effects such as drug toxicity, adverse drug reactions and drug resistance [3]. The term bioavailability enhancer was first used by the scientists at Indian Institute of Integrative Medicine (previously known as Regional Research Laboratory, Jammu, India) [4]. Bioavailability enhancer is also known as "Yogvahi" in Ayurveda. Yogvahi is used to improve the bioavailability particularly with low oral bioavailability and diminishing the unfavourable impacts of the drugs. Trikatu is used in many Ayurvedic formulations as it is known for its bioenhancing activity. Trikatu is a combination of three acrids namely black pepper (*Piper nigrum*), long pepper (*Piper longum*) and ginger (*Zingiber officinalis*) [5]. Indian spice, black pepper is the one of the herbals used in many Ayurvedic products. Several reports have shown that piperine has anti-hypertensive, anti-oxidant, anti-microbial properties apart from other medicinal values. Piperine was the first and most studied bioavailability enhancer in India [6,7]. The advantages of including bioenhancers in formulations are given in Figure 1. The known mechanisms of action of bioavailability enhancing agents are given in the Figure 2. Classification of bioenhancing agents based on origin and mechanisms of action are given in Table 1. The probable mechanisms of action of bioenhancing compounds are also given.

Bioenhancers of Indian Origin

Piperine

Piperine, a major alkaloid present in *Piper nigrum* (black pepper) and *Piper longum* (long pepper) belongs to the family *Piperaceae.* Piperine is responsible for pungency in both black and long pepper which is found in fruits and seeds. Apart from its role as a bioenhancer, piperine also exhibits anti-oxidant, anti-thyroid, [8] anti-platelet, [9] anti-hypertensive, [10] anti-tumor, [11] hepato-protective, [12] anti-inflammatory, [13] anti-asthmatic, [14] and fertility enhancer [15]. The chemical structure of piperine is given in Figure 3. Several studies showed that bioavailability enhancing ability of piperine is due to its interaction with drug metabolizing enzymes such as cytochrome P450 enzymes (CYP) and p-glycoprotein (drug efflux pump) that are involved in first pass elimination of many drugs. Piperine also inhibits other drug metabolic enzymes such as NADPH cytochrome C reductase, UDP-glucose dehydrogenase (UDP-GDH), aryl hydrocarbon hydroxylase (AHH) and UDP glucuronyl transferase [16].

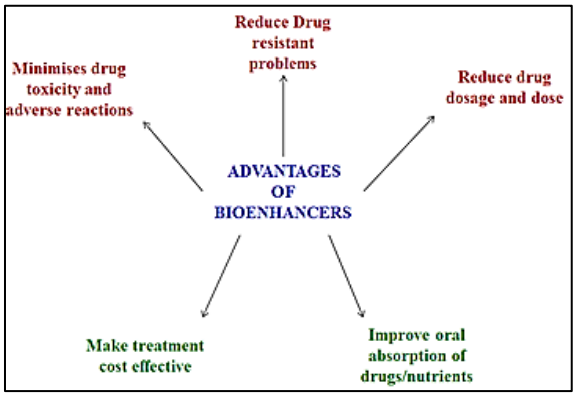


Figure 1: Advantages of using bioenhancers in pharmaceutical industry

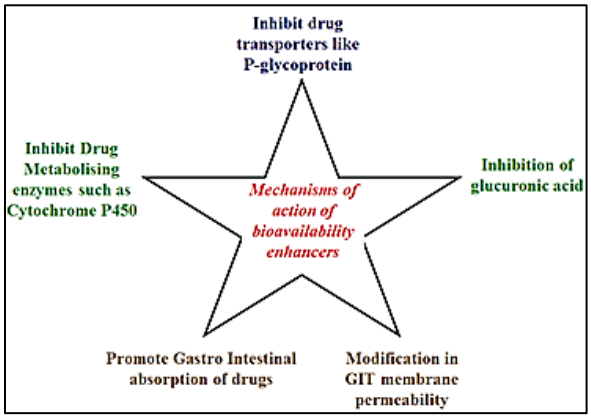


Figure 2: Mechanisms of action of bioenhancing compounds

Table 1: Bioenhancing compounds of plant and animal origin are given in the following table

Classification of bioenhancers based on their origin		
Bioenhancers of Plant Origin		**Bioenhancers of Animal Origin**
Piperine, Curcumin, *Carum carvi*, Stevia, Ginger, Allicin, Aloevera, Geinstein, Capsaicin, Quercetin, Naringin, Niaziridin, Liquorice, Lysergol, *Cuminum cyminum*		Cow Urine Distillate
Mechanisms of action of various bioenhancing compounds		
Inhibitors of P-glycoprotein efflux pump	**Inhibitors of Cytochrome P450 enzymes**	**Inducers of gastric absorption**
Piperine, Curcumin, *Carum carvi*, Genistein, *Cuminum cyminum*, Naringin, Quercetin	Piperine, Naringin, Gallic acid, Quercetin	Niaziridin, Liquorice, Ginger

Classes of the drugs whose bioavailability may be increased by piperine include antimicrobial agents, antiprotozoal agents, anti-helminthic agents, cardiovascular drugs, drugs acting on central nervous system, non-steroidal anti-inflammatory drugs, vaccines, vitamins, herbal compounds, anti-histaminics, respiratory drugs, anticancer drugs, corticosteroids, muscle relaxants and hormones etc. [17]. The following are the some of the studies on enhancement of bioavailability of several drugs when co-administered with piperine.

Piperine and Nevirapine

Piperine when co-administered with Nevirapine, a potent non- nucleoside inhibitor for HIV-1 reverse transcriptase, mean Cmax, AUCt, AUC0-∞ and Clast values of nevirapine were increased by approximately 120%, 167%, 170% and 146% respectively [18].

Figure 3: Several bioenhancing compounds present in Indian herbals

Piperine and Resveratrol

Effect of Piperine when co-administered with resveratrol Cmax and AUC of resveratrol was increased by 1544% and 229% [19].

Piperine with Propranolol

When Propranolol administered along with piperine, Cmax and AUC0-∞ of propranolol were increased by 100% and 102% [20].

Piperine and Beta-carotene

Piperine when co-administered with beta-carotene there was greater increase in serum β-carotene (49.8 ± 9.6 pg/dl vs. 30.9 ± 5.4 pg/dl) compared to β-carotene plus placebo. 60% greater increase of AUC was observed when piperine when co-administered with beta-carotene compared to β-carotene plus placebo [21].

Piperine and anti-TB drugs

When co-administered with piperine, several ant-tuberculosis drugs (Isoniazid and Pyrazinamide) had shown a greater increase of Cmax and AUC by 400% and 101% respectively [22]. Classes of Pharmaceuticals and Nutraceuticals Bioenhanced by piperine are given in Table 2.

Curcumin

Curcumin is biologically active flavonoid obtained from Indian spice turmeric (C*urcuma longa)*. Curcumin confers turmeric a bright orange – yellow color. Curcumin is used in dietary supplements, in beauty care products and as a food flavouring and colouring agent. The three curcuminoids present in turmeric are diferuloyl methane, desmethoxycurcumin and bisdemethoxycurcumin, volatile oils such as tumerone, atlantone, and zingiberone, sugars,

proteins and gums [23]. Several studies have shown that curcumin exhibits a variety of pharmacological actions such as anti-oxidant, anti-inflammatory, hepato-protective, nephro-protective, anti-carcinogenic, anti-microbial, hypo-glycemic and anti-rheumatic activities [24]. It supresses the drug metabolizing enzymes such as CYP3A4, down-regulates p-gp and improves the Cmax and AUC of several anti-hypertensive and anti-anxietic drugs. Curcumin also inhibits UDP- glucuronyl transferase in gastro-intestinal tissues. Curcumin when co-administered with norfloxacin increased AUC and decreased the maintenance dose.

Table 2: The bio-availability of the drugs mentioned above are increased when these drugs are administered along with piperine

Class	Examples
Water soluble vitamins	Vitamin B1, Vitamin B2,niacinamide, Vitamin B_6, Vitamin B_{12}, folic acid and vitamin C
Fat soluble vitamins	Vitamin A, D, E and K
Amino acids	Lysine, Isoleucine, Leucine, Threonine, Valine, Tryptophan, Phenylalanine and Methionine
Minerals	Iodine, Calcium, Iron, Zinc, Copper, Selenium, Magnesium, Potassium, and Manganese
Herbal constituents	Boswellic acid (*Boswellia serrata*), Ginsenosides (*Gingko biloba*), Withanaloids (*Withania somnifera*), Curcuminoides (*Curcuma longa*), and Pycnogenol (*Pinus pinaster*)
Antioxidants	Vitamin A, Vitamin C, Vitamin E, Alpha carotene, Beta carotene, Beta crypto xanthine, Lycopene, Lutein, Polyphenols
Antimicrobial agents	Ciprofloxacin, Pefloxacin, Ofloxacin, Norfloxacin, Phenoxymethyl Penicillin, Ampicillin, Amoxicillin, Cloxacillin, Erythromycin, Roxithromycin, Azithromycin, Cephalexin, Cefadroxil, Cefuroxime axetil, Cefixime, Co-trimoxazole, Acyclovir, Cefaclor, Clofazimine, Fluconazole, Griseofulvin, Ketoconazole
Antiprotozoal agents	Metronidazole, Tinidazole, Quinine, Chloroquine, Primaquine, Sulfadoxine + Pyrimethamine
Anthelmintic agents	Mebendazole
Cardiovascular drugs	Amlodipine, Diltiazem, Atenolol, Lisinopril, Lovastatin, Gemfibrozil, Nifedipine, Enalapril, Propranolol
Drugs acting on central nervous systems	L-dopa, Buspirone, Dextropropoxyphene, Pentazocine, Morphin derivatives, Diazepam, Lorazepam, Alprazolam, Haloperidol, Chlorpromazine, Thioridazine
Non-steroidal anti-inflammatory drugs	Diclofenac, Ketorolac, Piroxicam, Ibuprofen, Indomethacin, Naproxen
Drugs used in the treatment of respiratory disorders	Solbutamol, Terbutaline, Theophylline, Bromhexine
Antihistaminics	Astemizole, Terfenadine, Loratadine
Prokinetic drugs	Metoclopramide, Domperidone, Cisapride
Corticosteroids	Prednisolone, Dexamethasone, Betamethasone
Steroid hormones	Stanazolol, Oral Contraceptives
Vaccines	Oral polio vaccine
Antiulcer drugs	Omeprazole, Ranitidine, Femotidine etc.
Central muscle relaxants	Carisoprodol, Chlormezanone
Anti-Cancer Drugs	
1) Alkylating agents	Mechlorthiamine, Cyclophosphamide, Ifosamide, Chlorambucil, Hexamethylmelamine, ThiotepaBusulfan,
2) Antimetabolites	Carmustine, Lomustine, Semustine, Streptozotocin, Decarbazine, Vincristine,Vinblastin, Etoposide, Teniposide, Dectinimycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin,Bleomycin,
3) Natural Products	Mithramycin, Mitomycin, L- Asparaginase, Interferon Alfa
Hormone and hormone antagonists	Prednisolone, Hydroxyprogestirone, Medroxyprogestirone, Megestrol, Diethylstilbestirole, Ethinyl estradiol, Tamoxifen, Testosterone propionate, Fluoxymesterone, Flutamide, Leuprolide
Miscellaneous agents	Cisplatin, Crboplatin, Mitoxantrone, Hydroxyurea, Procarbazine, Mitotane, Aminoglutethimide, Coenzyme Q10

Gingerol

[6]-gingerol is the major pungent essential oil of ginger (*Zingiber officinale*). Gingerol improves the absorption of several drugs by regulating the intestinal function to facilitate absorption of several drugs. Gingerol alone provides bio enhancing activity in the range of 30-75%, whereas piperine and gingerol combination provide the bioavailability of drugs in the range of 10–85%. The bioenhancing dosage of gingerol is in the range of 10–30

mg/kg body weight and piperine is in the range of 4-12 mg/kg body weight. It increases the bioavailability of several antibiotics like Azithromycin, Erythromycin, Cephalexin, Cefadroxil, Cloxacillin, and Amoxycillin [25-27].

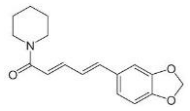
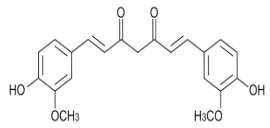
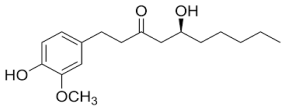
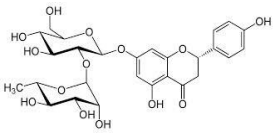
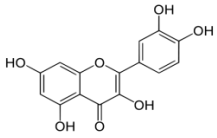
Naringin

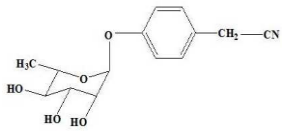
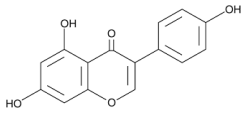
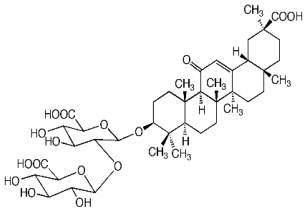
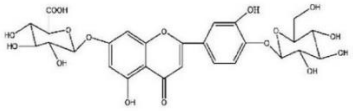
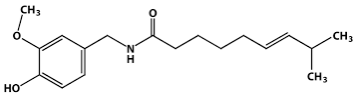
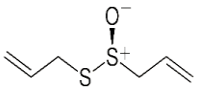
Naringin is a major flavonoid found in grapefruits, sour oranges, onions, apples and tea. It exhibits various pharmacological effects such as anti-oxidant, anti-allergic, lowering blood lipid level and anti-carcinogenic. Naringin has shown inhibitory activity of several drug metabolizing enzymes such as CYP3A1, CYP3A2, and CYP3A4 and additionally modulates p-gp drug efflux pump. This mechanism of action made naringin to increase the bioavailability of drugs such as paclitaxel, verapamil, saquinavir and cyclosporine A, tamoxifen, doxorubicin and diltiazem [27].

Quercetin

Quercetin is a plant derived flavonoid found in apples, onions, nuts, berries, broccoli [28-30]. It displays significant properties like anti-viral, anti-carcinogenic, anti-bacterial and anti-inflammatory [31], anti-oxidant, free radical scavenging effects [28]. It also acts by inhibiting drug metabolizing enzymes, CYP3A4 and drug transporter pump, p-glycoprotein [29]. The bioavailability enhancement effect of quercetin was well studied on oral administration of paclitaxel when co-administered with quercetin [27]. Allicin, Capsaicin, Caraway, Cumin, Genistein, Liquorice and Niaziridin are several plant based compounds known to increase the bioavailability of several anti-microbial, anti-cancer, anti-hypertensive and anti-diabetic drugs. In Table 3, different drugs whose bioavailability may be increased when co-administered with the bioenhancing compounds are given.

Table 3: The following table represents the source and structural representation of several bioenhancing compounds of Indian origin

S. No	Source of bioenhancer	Bio enhancing compound	Structure	Drugs whose Bioavailability may be enhanced
1	Black pepper (*Piper nigrum*), Long pepper (*Piper longum*)	Piperine		Reserveratol, Phenytoin, Nevirapine, Rifampicin, Theophylline, Polyphenols etc.
2	Turmeric	Curcumin		Midazolam, Celiprolol, Norfloxacin
3	Ginger *(Zingiber officinale)*	[6]- Gingerol		Azithromycin, Erythromycin, Cephalexin, Cefadroxil, Ketoconazole, Cloxacillin, and Amoxycillin
4.	Citrus fruits	Naringin		Paclitaxel, Verapamil, Saquinavir, Cyclosporine A, Tamoxifen, Doxorubicin and Diltiazem
5	Apples, onions, nuts, berries, broccoli and grains	Quercetin		Paclitaxel, Verapamil, Tamoxifen, Fexofenadine, Etoposide, Polyphenols and Doxorubicin

6	Drumstick leaves, pods and bark	Niaziridin		Rifampicin, Ampicillin, Tetracycline, and Nalidixic acids
7	Soyabeans, lupin and kudzu	Genistein		Polyphenols, Paclitaxel
8	Liquorice (*Glycyrrhiza glabra*)	Glycyrrhizin		Rifampicin, Ampicillin, Tetracycline, and Nalidixic acids
9	Cumin *(Cuminum cyminum)*	3',5dihydroxy flavone-7-O-β-D-galactouronide-4'-β-O-D-glucopyranoside		Cycloserine, Amoxicillin and Erythromycin, Fluconazole, Zidovudine and Cephalexin
10	Chilli pepper (*Capsicum annum)*	Capsaicin		Theophylline
11	Garlic (*Allium Sativum*)	Allicin		Amphotericin B

Bioenhancers of Animal Origin

Cow urine distillate

According to Ayurveda literature, cow urine (*Gomutra*) is useful in the treatment of number of diseases such as leprosy, filaria, cancer etc. [32]. Cow urine contains all compounds that are necessary for the functioning of the body such as water, urea, vitamins A, B, C, D, E, minerals, enzymes and hormones [33]. Cow urine distillate is more effective as bioenhancer than cow urine, to increase the bioavailability of antimicrobial, antifungal, and anticancer drugs. Cow urine distillate enhances the absorption and transport of several drugs by inhibiting the drug metabolising enzymes and drug transporter proteins across cell membranes. Cow urine distillate increased the activity of antibiotics by 5-7 times against *Escherichia coli* and 3-11 times against Gram-positive bacteria, by enhancing the transport of antibiotics across the gastrointestinal tract. Rifampicin tetracycline, ampicillin and zinc are some of the drugs whose bioavailability was increased when co-administered with cow urine distillate [27,34]. Cow urine distillate enhanced the levels of gonadotropin releasing hormone. Due to this, gonadosomatic indices, sperm motility, sperm count, and sperm morphology were enhanced [35].

CONCLUSION

The current paper discussed the bioavailability enhancing effects of natural products in animals and humans. But these compounds have not been completely explored till date. But the information on the exact mechanism of action, toxicity evaluation and suitable drug combinations are to be assessed. The effective formulation strategy of natural products is crucial to improve their *in vivo* performance and ultimately maximize their effectiveness as a

bioavailability enhancer. Some of the natural products discussed in this paper are piperine, curcumin, gingerol, niaziridin, glycyrrhizin, cumin, caraway, allicin, genistein, capsaicin, quercetin, naringin, and cow urine distillate. These compounds reduce the dose, shorten treatment, and thus reduce drug-resistance and drug toxicity or adverse reactions. Due to dose economy, treatment is cost-effective. Therefore, it is important to focus on this area for further research on their active principles, mechanisms of actions, toxicity evaluation, and suitable combinations with other drugs. This will help us to explore novel principles with high bioenhancing ability and less toxic effects.

ACKNOWLEDGEMENTS

The review is based on the research work conducted during University Grants Commission (UGC) sponsored project (F. No. 42-221/2013 SR).

REFERENCES

[1] DB Brahmanka; S Jaiswal. Biopharmaceutics and Pharmacokinetics: A Treatise (1st edn). Vallabh Prakashan Publishers, **1995**, 24-26.
[2] VD Tatiraju; VB Bagade; JP Karambelkar; MV Jadhav; V Kadam. *J Pharmacognosy Phytochem*. **2013**, 2(3), 55-60.
[3] SS Muttepawar; SB Jadhav; AD Kankudate; SD Sanghai; DR Usturge; S Chavare. World J Pharm Sci, **2014**, 3(3), 667-677.
[4] N Atal; KL Bedi. *J Ayurveda Integr Med*. **2010**, 1(2), 96-99.
[5] GK Randhawa; JS Kullar; Rajkumar. Int J App Basic Med Res. **2011**, 1(1), 5-10.
[6] S Drabu; S Khatri; S Babu; P Lohani. *Res J Pharm Biol Chem Sci*. **2011**, 2(4), 108-119.
[7] XF Grace; SL Seetha; D Chamundeeswari; PK Manna; S Shanthi; S Latha. *Indo American J Pharm Res*. **2013**, 3(12), 1576-1580.
[8] RK Vijaya; N Nalini. *J Basic Clin Physiol Pharmacol*. **2006**, 17(2), 71-86.
[9] B Park; D Son; Y Park; T Kim; S Lee. *Phytomedicine*. **2007**, 14(12), 853-855.
[10] S Taqvi; A Shah; A Gilani. *J Cardiovasc Pharm*. **2008**, 52(5), 452-458.
[11] S Manoharan; S Balakrishnan; V Menon; L Alias; A Reena. *Singapore Med J*. **2009**, 50(2), 139-146.
[12] H Matsuda; K Ninomiya; T Morikawa; D Yasuda; I Yamaguchi; M Yoshikawa. *Bioorg Med Chem Lett*. **2008**, 18(6), 2038-2042.
[13] S Kumar; V Singhal; R Roshan; A Sharma; G Rembhotkar; B Ghosh. *Eur J Pharmacol*. **2007**, 575(1-3), 177-186.
[14] S Kim; Y Lee. *J Pharm Pharmacol*. **2009**, 61(3), 353-359.
[15] P Piyachaturawat; C Pholpramoolz. *Cell Biol Int*. **1997**, 21(7), 405-409.
[16] SG Acharya; AH Momin; AV Gajjar. *Am J Pharm Tech Res*. **2012**, 2(2), 32-44.
[17] RB Patel; IA Modi. Inventors, Cadila Laboratories Limited, assignee. Compositions containing piperine, United States patent US 5,616,593. **1997**.
[18] R Kasibhatta; MU Naidu. *Drugs R & D*. **2007**, 8(6), 383-391.
[19] JJ Johnson; M Nihal; IA Siddiqui; CO Scarlett; HH Bailey; H Mukhtar; N Ahmad. *Mol Nut Food Res*. **2011**, 55(8), 1169-1176.
[20] G Bano; RK Raina; U Zutshi; KL Bedi; RK Johri; SC Sharma. *Eur J Clin Pharmacol*. **1991**, 41(6), 615-617.
[21] V Badmaev; M Majeed; EP Norkus. *Nut Res*. **1999**, 19(3), 381-388.
[22] RS Kapil; U Zutshi; KL Bedi. *Eur Patent*, **2002**.
[23] M Akram; S Uddin; A Ahmed; K Usmanghani; A Hannan; E Mohiuddin. *Rom J Biol Plant Biol*. **2010**, 55(2), 65-70.
[24] P Anand; AB Kunnumakkara; RA Newman; BB Aggarwal. *Mol Pharm*. **2007**, 4(6), 807-818.
[25] GN Qazi; KL Bedi; RK Johri. Bioavailability enhancing activity of *Zingiber officinale* and its extracts/ fractions thereof, United States Patent Number, US2003/ 0170326A1, **2003**.
[26] G Qazi; K Bedi; R Johri; M Tikoo; A Tikoo; S Sharma; S Abdullah; O Suri; B Gupta; K Suri; N Satti. Inventors. Bioavailability enchancing activity of Zingiber officinale Linn and its extracts/fractions thereof. United States patent application US 10/318,314. **2002**.
[27] GB Dudhatra; SK Mody; MM Awale; HB Patel; CM Modi; A Kumar. *Sci World J*. **2012**, 1, 1-33.
[28] P Lakhanpal; DK Rai. *Int J Med Update*. **2007**, 2(2), 22-37.

[29] MJ Kang; JY Cho; BH Shim; DK Kim; J Lee. *J Med Plants Res*. **2009**, 3(13), 1204-1211.
[30] B Jhanwar; G Somdatt. *Int J Pharm Tech Res*. **2014**, 6, 443-454.
[31] PV Naidu; PM Kinthada; P Kalyani; P Muralidhar. *Int J Pharm*. **2012**, 3, 24-27.
[32] J Edwin; E Sheej; T Vaibhav; G Rajesh; T Emmanuel. *Global J Pharmacol*. **2008**, 2(2), 20-22.
[33] V Sai Kishore; RL Rao. B Ramesh; K Aditya. *Mintage J Pharm Med Sci*. **2015**, 4(1),1-4.
[34] SP Khanuja; S Kumar; AK Shasany; JS Arya; MP Darokar; M Singh. The inventors. Pharmaceutical composition containing cow urine distillate and an antibiotic. United States patent US 6,410,059. **2002**.
[35] JA Ganaie; V Gautam; VK Shrivastava. *J Reprod Fertil*. **2011**, 12(1), 3-7.