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Phyto-phospholipid complex: A tabular update

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Abstract

Phytoconstituents have been used in medicine science since ancient times due to their various pharmacological actions. But most of them (like flavanoids, terpenoids) are low in lipid solubility and have large molecular size due to complex multiple ring structure, causing poor absorption and poor bioavailability via oral route. The phytosome system of drug delivery results in increased bioavailability of these phytoconstituents. Phytosome are produced by a patented process where standardized plant extracts/phytoconstituents are bound to phospholipids (mostly phosphatidylcholine). The phytosome technology has been applied over many popular herbal drugs such as Ginkgo biloba, hawthorn, milk thistle, grape seed, green tea and ginseng.

Key Words: Phytosomes, Phytoconstituents, Phytophospholipids.

INTRODUCTION

Various phytochemical and pharmacological studies have established the biological activities and therapeutic benefits of numerous plant extracts. But it was found that conventional herbal extracts had a considerable loss of activity on isolation and purification.Thus standardization of herbal extracts was done. Though standardized plant extracts were established, their clinical efficacy was limited due to poor bioavailability [1,2].

Often extracts when taken orally, some phytoconstituents get destroyed in gut environment resulting in poor bioavailability. Also,poor absorption of phytoconstituents like flavanoids and terpenes is due to factors like low lipid solubility and multiple ring polyphenolic structures. Multiple ring molecules are large in molecular size and hence cannot be absorbed by simple diffusion. On the other hand, low lipid affinity/solubility of these phytoconstituents does not allow them to pass across cell membranes as cell membranes are lipid rich [3]. It has been found

that conventional herbal extracts when complexed with phospholoipids have improved bioavailability.Thus the problem of poor absorption of phytoconstituents like flavanoids has been overcome by Phytosome technology. [4]

Table: Various research in the field of phyto-phospholipid complexes

S. No.	Researcher(s)/ Work on	Work summary	Result/Conclusion(s)
1	Gabetta et al. (1989)- Silymarin	- Work was done on silymarine. -Purified silybin was complexed with PC.	Resultant molecular complex showed increased solubility in lipophilic, organic solvents. [5]
2	Barzaghi et al. (1990) – IdB1016 (silymarin phytosome)	They studied pharmacokinetics in healthy human volunteers by monitoring silybin plasma levels after oral administration of single doses of IdB1016 and silymarin to a group of 9 volunteers. Subsequently, 9 healthy volunteers were given 120 mg IdB1016 twice a day for 8 days.	Compared to simple extract, silybin-PC phytosome showed 4.6 times increase in its oral bioavailability probably by facilitating its passage across gastrointestinal mucosa. [6]
3	Malandrino et al. (1990)- IdB1016	Silymarin extract was complexed with soy PC.	Improved bioavailability of silybin. [7]
4	Comogilo et al. (1990)- IdB1016	1.5g/kg body weight IdB1016 was administered intragastrically in rats and after one hour of administration, concentration of silybin in liver microsomes was estimated using microsomal suspension of 10 microM. Free radical trapping property was estimated by spin trapping experiments.	Free radicals were trapped within hepatocytes by silybin from silipide. [8]
5	Orlando et al. (1990)- silymarin phytosome	Short term experiment- 9 patients with liver cirrhosis were given high dose-360 mg of silybin phytosome for one day.	High inter-patient variability for hepatoprotective activity, no adverse effects. [9]
6	Mareno and Lampertico (1991)- Silipide (silymarin phytosome)	Serum levels of liver enzymes- aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gammaglutamyl-transpeptidase (GGT) were studied by- a) 360 mg silipide phytosome was given to healthy volunteers, three times a day for three weeks. b) 240 mg/360 mg was given daily for 4 months to 232 patients with liver disorders.	a.No adverse effect was reported. b.Excellent tolerability of silypide phytosome was found.Minor adverse effects- nausea, heartburn, dyspepsia, transient headache, were found in 5.2% patients, in comparison to 8.2% patients (those treated with non complexed silybin) and 5.1% patients treated with

			placebo. [10]
7	Bombardelli et al. (1991)- Silymarin phytosome	Percent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties of silymarin-PC complex were studied.	Compared to single components of silymarin, silymarin phytosome showed increase in duration of action and specific activity. [11]
8	Pifferi et al. (1991)- Silipide	Animal models of hepatic injury were studied.	Compared to simple silybin , silybin complex-silipide showed higher pharmacological activity with increased bioavailability (oral) and specific organ targeting nature of silybin. [12]
9	Orlando et al. (1991)- IdB1016	10 patients with compensated liver cirrhosis (Child's Grade A) were given single daily dose of 120 mg, followed by multiple dose-120 mg twice a day for eight days. Their blood silybin levels were monitered.	There was no significant difference in data of eight-day dosing and first day dosing, indicating that silybin was not accumulating in poorly functioning livers. Also, no adverse effects were reported. [13]
10	Morazzoni et al. (1992)- Siliphos[R] (silymarin phytosome)	Comparison of pharmacokinetics of silipide and silybin was studied in rats. A single oral dose of 200 mg per kg body weight was given and biliary & urinary silybin excretion as well as unconjugated & total plasma silybin levels were measured.	Silybin from phytosome remained elevated at 70 hours after oral dosing whereas simple silybin was barely above detectable level even after 25 hours of dosing, indicating improved gastrointestinal absorption and oral bioavailability of IdB1016. [14]
11	Carini et al. (1992) – IdB1016	Rat hepatocyte model was used. Lipid peroxidation was induced by cumene hydroperoxidase in isolated rat hepatocytes, followed by addition of IdB1016 in increasing concentrations.	IdB1016 caused dose dependant lipid peroxidation inhibition. So, free radical mediated toxic hepato injury treatment can use IdB1016 as protective agent. [15]
12	Conti et al. (1992)- IdB1016	a.They studied protective activity of silybin by testing IdB1016 in rodents with liver damage. b. Comparitive study of protective activity of silybin,phosphatidylcholine and their complex-IdB1016.	a. Dose related protective effect against hepatotoxicity caused by carbon tetrachloride, ethanol, praseodymium and galactosamine. b. At same dose, IdB1016 showed protective activity

			against paracetamol induced hepato-toxicity, whereas simple silybin or phosphatidylcholine didn't show any. [16]
13	Marcelli et al. (1992)- IdB1016	They studied patients with biopsy confirmed chronic persistent hepatitis. Randomly selected 31 patients were given 240 mg silybin phytosome and 34 patients were given placebo, one capsule orally, twice a day for three months.	a.Group with phytosome showed significant decrease in serum level of ALT and AST whereas placebo group showed worsened enzyme indicators(AST,ALT) a. Phytosome treatment was well tolerated.No adverse effect is in phyto-some treated patients, few adverse effects in placebo group. [17]
14	Schandalik et al. (1992)- Silipide	9 patients who had a surgical removal of gall bladder due to gall stones were given single oral doses of 120 mg silybin phytosome or silymarin and bile was monitored	Peak level of silybin in bile was attained in 4 hours. Also,after 48 hours, silybin recovered in bile was 11 % from phytosome whereas approximately 3% from simple silymarin. Thus, phytosomal silybin has 4 times greater passage through liver than simple silybin. [18]
15	Buzzeli et al. (1993)- IdB1016	Short pilot study was carried out on 20 patients with chronic active hepatitis (CAH). Randomly chosen 10 patients (4male 6 female with average age 50 years) were given 240 mg silybin twice a day and 10 patients (2 male 8 female with average age 55 years) were given placebo. Before and after 7 days of treatrment, blood samples were taken and tested for liver function tests (LFT) , malonaldehyde (indicator of lipid peroxidation) and coper & zinc (indicators for free radical mediated lipid peroxidation).	Mean serum concentration of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltrans-peptidase (gamma-GT) were reduced significantly and total bilirubin and alkaline phosphate levels were reduced slightly with no significant reduction in malonaldehyde, copper and zinc levels. This indicated the increased membrane permeability in patients with CAH and improved LFTs (related to hepatocyte necrosis) by IdB1016. [19]
16	Vailati et al. (1993)-	They carried out a phase 2 clinical trial in patients with viral and	Treatment with silymarin phytosome showed dose

	IdB1016	alcoholic hepatitis.	dependant improved condition. [20]
17	Moscarella et al. (1993)- Silybin phytosome (silymarin phytosome)	A short pilot study was performed with 8 patients of chronic active hepatitis-B and/or C. Patients were treated with 240 mg of silybin-PC complex daily.	Decrease in levels of hepato enzymes ALT and AST. Minor reduction in levels of glutamyl transpeptidase (GGT) and malondialdehyde (MDA)- byproduct of lipid peroxidation. [21]
18	Morazzoni et al. (1993)- Siliphos[R]	Siliphos[R] and silymarin were given to rats in a dose of 200 mg per kg body weight and biliary excretion of silybin and its plasma levels were monitored and silybin was assayed by a specific HPLC method.	Detectable level of silybin in plasma was reached within minutes, with peak level gained in 1 hour and elevated levels maintained for more than 6 hours.Also, phytosomal silybin as compared to simple silybin, reached liver and to bile in 2 hours i.e.6.5 times faster (13% versus 2% in 24 hours). [22]
19	Schwitters et al. (1993)- Grape seed phytosome	They complexed oligomeric polyphenols i.e. procyanidins from *Vitis vinifera* of varying molecular size with phospholipids, and studied it for various applications.	Procyanidins from grape seed phytosome showed high antioxidant property, and have cardiovascular protective effect (protection against atherosclerosis and heart damage due to ischemia/ reperfusion [23].
20	Facina et al. (1994)- Grape seed phytosome	a.) In pre-clinical trial, a high cholestrol diet was fed to rabbits for 6 weeks to increase blood cholestrol and induce atherosclerotic lesions in their aortas and carotid arteries. One group of rabbits was then given grape seed phytosome for 6 weks and high cholestrol diet in following 4 weeks. Another group was given conventional grape seed extract in same manner. b.) In clinical trial, random young healthy human volunteers were given grape seed phytosome once daily for five days and control received conventional grape seed extract. Their blood TRAP (Total Radical trapping Antioxidant	a) Group with phytosomal grape seed extract showed less aortic plaque than conventional grape seed extract. b) As compared to conventional extract, phytosomal grape seed extract showed elevated blood TRAP evel after 30 minutes of administration on 1st day itself.

		Parameter) was measured several times on 1st and 5th day.	[24]
21	Comoglio et al. (1995)- Silipide	Effect of silipide was studied on ethanol derived free radicals.	It has antioxidant and free radical (alcohol derived) scavenging properties, thus useful in treatment of free radical mediated injury in alcohol induced liver damage. [25]
22	Nuttall et al. (1998) – Leucoselect-phytosome (grape seed extract phytosome)	(Randomized single blinded, cross over study) for 5 days 20 young volunteers were given 2 capsules containing 300 mg of leucoselect phytosome or placebo (randomly) daily. Blood samples taken at 1st & 5th day were assayed for antioxidant activity and vitamin C & E levels. After two weeks (wash out period) study was repeated with 2nd treatment (those who received phytosome 1st , were now given placebo and vice-versa).	No effect on vitamin C & E levels, but there was an increase in serum total antioxidant activity. [26]
23	Pietta et al. (1998)- Greenselect Phytosome (green tea phytosome)	Human volunteers were given single dose (equivalent to 400 mg of epigallocatechingallate i.e. ECG) of greenselect (free catechins of green tea) and greenselect phytosome (phospholipid complex). Time course plasma concentration of ECG was correlated to subsequent percent variations of ascorbate, total glutathion, alpha tocopherol, beta carotene and total radical antioxidant parameter (TRAP) in plasma.	Absorption of green tea catechins (possesing radical-scavenging, metal chelating and enzyme modulation ability) from phytosome was more than as free catechins. [27]
24	Grange et al. (1999)- Silymarin phytosome	50 female Fisher/344 rats were divided in 5 treatment groups. Group 1 was given liquid diet of dextrin maltose of isocaloric amount to the caloric amount of ethanol diet. Group 2 was given diet to which 400mg/kg silymarin i.e. SY (29.8% silybin complexed with phosphatidyl-choline) was added.Group 3 was given a liquid diet with both SY and 35% ethanol	Fetoprotectant activity against alcohol induced damage to corpus callosum development in brain was reported. [28]

		derived calories(EDC). Group 4 was given only 35% EDC, and group 5 was given unlimited access to Purina lab chow. Laterality testing of offspring was done at the age of 12 weeks. Then rats were sacrificed and brains were perfused for corpus callosum extraction.	
25	Maffei Facino et al. (1999)- Leucoselect phytosome	Young and aged rats were given Leucoselect phytosome- 2.4% concentration in a standard diet for 3 weeks.	An increase in TRAP, decrease in coronary perfusion pressure was observed, indicating improved antioxidant activity and cardiovascular protective activity respectively. [29]
26	Jiang et al. (2001)- Herba Epimedii flavanoids phytosome (EFP)	They optimized preparation techniques for EFP. EFP was prepared by solvent evaporation, accumulated dissolution of different ratios of EFP-PVP precipitates were studied and step regression and uniform design lead to optimized preparation conditions as follows : solvent = tetrahydrofuran, lecithin to PVP--2.5 times, temperature = 40 degree centigrade and reaction time = 3 hours.	Accumulative dissolution of Herba Epimedii flavanoids from EFP-PVP precipitate was higher than simple Herba Epimedii flavanoids indicating improvement in dissolution due to PVP. Also, phospholipid enhanced oil/water apparent partition coefficient of icariin by more than 4 times. [30]
27	Mauri et al. (2001)- Ginkgoselect phytosome	160 mg of simple extract of Ginkgo biloba and ginkgoselect phytosome (same dose) were given to two groups (randomly divided) of total 15 healthy volunteers. After 1 week (wash out period), both groups switched treatments.blood samples were collected at regular intervals and liquid chromatography, atmospheric chemical ionization and mass spectrometry were used for detection of terpene lactone.	Absorption of ginkgolides A & B from phytosome was 3.5 times higher than from simple extract. [29]
28	Carini et al. (2001)- Ginkgoselect phytosome	5 rats were given simple extract of Ginkgo biloba (300 mg/kg) and Ginkgoselect phytosome (same dose) daily. FRAP i.e. ferric reducing ability of plasma method was used to determine total plasma antioxidant capacity and brain antioxidant capacity in rats with	Total plasma antioxidant capacity in rats by phytosome was higher (27.9%) than simple extract. [29]

		ginkgoselect phytosome,and Ginkgo biloba extract and in control group.	
29	Jiang et al. (2002)	4 month old panther's rats (ovaries on both sides were castrated) were used for osteoporosis model. Bone density was determined by dual energy X-rays and, estradiol & IL-6 serum concentrations were assayed by immunity and ELASA respectively and their effects were determined.	EFP improved bone density, increased E2 and decresed IL-6 concentration in serum. [31]
30	Busby et al. (2002)-Silymarin phytosome	A group of pregnant Sprague-Dawley rats was given liquid diet containing 35% ethanol derived calories (EDC). Another group was given liquid diet containing both 35% EDC and silybin/phospholipid compound (SI). Offspring were tested on social recognition task and on radial arm maze at the age of 90 & 75 days respectively.	As compared to simple siymarin extract, phytosome showed improve fetoprotectant activity against ethanol induced behavioral deficits. [32]
31	Ursini et al. (2002)-Leucoselect phytosome	A group of rabbits was given 0.25% cholesterol rich diet whereas another group was given leucoselect phytosome with same diet as group1.	Atherosclerotic aortic lesions were reported in cholesterol diet group, whereas a significant reduction in aortic lesions was reported in group provided with leucoseect phytosome, indicating antiatherosclerotic activity of leucoselect phytosome. [29]
32	Muir et al. (2002) – Ginkgoselect phytosome	Double blind, placebo-controlled trial.22 subjects having Raynaud's disease were given 120 mg three times a day(360 mg). Frequency,duration and severity of any vasopastic attack were recorded.patients were reviewed after 2,4 and 10 weeks of treatment.	Ginkgoselect phytosome showed considerable decrease in frequency and severity of Raynaud's attacks as against placebo. [29]
33	Natella et al. (2002)-Leucoselect-phytosome	8 healthy volunteers were 1st provided with lipid peroxides rich,fatty meal (Milanese steak and French fries). After 1 week they were given same meal with leucoselect phytosome. Lipid hydroperoxides concentration in plasma was determined.	An increase in TRAP (Total Radical trapping Antioxidant Parameter), improved resistance of low densilty lipids against oxidative modification and a significant reduction in plasma lipid hydroperoxides was reported.

			[29]
34	Vigna et al. (2003)- Leucoselect-phytosome (LP)	(Randomized, double-blind, crossover study) In phase 1, 24 healthy human male (heavy smokers, age = 50 years or more) were given 2 capsules (containing 75 mg of LP or placebo i.e. 75 mg lactose with soy-PC) twice a day for 4 weeks. After 3 weeks (wash out period), phase 2 started in which those who received LP in phase 1 were now given placebo and vice-versa for another 4 weeks. Blood samples were taken at the start and end of each phase and assayed for plasma lipids and low-density lipoprotein (LDL) susceptibility to oxidation.	Good compliance, no adverse effects, and no significant modification of total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C) and LDL-C. Also, in subjects treated with LP, reduction in thiobarbituric acid reactive substances (TBARS) concentration was reported, indicating LP's potential use in oxidative stress condition (smoking) due to its antioxidant property. [33]
35	Tedesco et al. (2004)- Silymarin phytosome	21 commercial broiler chickens of 14 days age were divided in 3 groups. Group C (control) was given basal diet, group B1 was given aflatoxin B1 (AFB1) at 0.8 mg/kg of feed and group BW was given AFB1 at 0.8 mg/kg of feed with silymarin phytosome at 600 mg/kg of BW.	Silymarin phytosome was found to be hepatoprotective against negative effects of AFB1 on performance of broiler chicks. [34]
36	Maiti et al. (2005)- Quercetin-pytosome	Using carbon tetra chloride, liver injury was induced in rats, which were then treated with quercetin phytosome.	Phytosome formulation showed improved therapeutic efficacy than simple quercetin. [35]
37	Yanyu et al. (2006)- Silymarin phytosome	Silybin and phospholipids were resolved into ethanol, which was removed under vacuum to form silybin-phospholipid complex. Its physicochemical properties like scanning electron microscopy (SEM), transmission electron microscopy (TEM), differential scanning calorimetry (DSC), solubility, dissolution, etc. were tested. RP-HPLC was used to determine concentrations of silybin after oral administration of silybin-	Phytosome preparation showed increased bioavail-ability (oral administration) ,improved biological effect of silybin. [36]

		phospholipid complex and silybin-N-methylglucamine at different time in rats.	
38	Maiti et al. (2006)- Curcumin-phospholipid complex	Acute liver damage was induced in rats by carbon tetra chloride. They were then treated with 100 & 200 mg of curcumin phytosome and free curcumin (same doses). Various enzymes in oxidative stress condition were measured and thus antioxidant activity was evaluated.	As compared to free curcumin, serum concentration of curcumin from phytosome was higher (Cmax = 0.5 mcg/ml and 1.2 microg/ml respectively, equivalent to 1.0 g/kg of curcumin) indicating improved absorption.Also, phytosome preparation showed improved hepato-protective activity than simple curcumin. Also, phytosomal curcumin showed slower elimination than free curcumin (indicated by effective concentration of curcumin for a longer period of time in rat serum by phytosome). [37]
39	Maiti et al. (2006)- Naringenin-phospholipid complex	Rats were intoxicated by carbon tetra chloride and then treated with 100 mg /kg body weight naringenin phytosome and free naringenin (same dose). Antioxidant potential was evaluated by measuring liver enzymes-glutathione peroxidase, superoxide dismutase, catalase and thiobarbituric acid reactive substances. Naringenin concentration in plasma was also determined and serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, serum alkaline phosphatase and total bilirubin were determined for Liver function tests.	Phytosome preparation showed better hepato-protective and antioxidant activity and showed longer duration of action than free naringenin indicating its slower elimination. [38]
40	Naik et al. (2006)- Ginkgo biloba phytosome	Wistar rats were given Ginkgo biloba phytosome in dose of 50 mg/kg body weight for 7 days and 100 mg/kg body weight for 14 days. After 1 hour of the last dose of phytosome, 75 mg/kg sodium nitrite was given to rats to induce hypoxia.	The antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase) were increased in phytosome treated rats (in comparison to rats given

		After 30 more minutes, rats were sacrificed to isolate and homogenise cerebral cortex, cerebellum, hippocampus and striatum. Superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase were estimated from supernatants.	sodium nitrite only) indicating prevention of depletion of the anti-oxidant enzymes by sodium nitrite in the presence of Ginkgo biloba phytosomes. [39]
41	Naik et al. (2008) – Ginkgoselect phytosome (Ginkgo biloba phytosome,GB)	Wistar rats were given rifampicin i.e. RMP (500 mg/kg, p.o.) daily for 30 days to induce liver damage. Simultaneously 25 mg/kg and 50 mg/kg of GBP and 100 mg/kg silymarin (reference drug) were given orally for 30 days daily to RMP treated rats. Marker enzymes-serum glutamate oxaloacetate transaminase(SGOT), serum glutamate pyruvate transaminase(SGPT), serum alkaline phosphatase (SALP) and albaumin (Alb) and total proteins (TP) serum levels were determined. Also, the effects of GBP on lipid peroxidation (LPO), reduced levels of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and glutathione reductase (GR) were assayed in liver homogenates.	GBP (and reference drug silymarin) showed significant hepatoprotective activity indicated by reduction in serum marker enzymes (SGOT, SGPT and SALP) lipid peroxidation, and dose dependant increase in GSH, SOD, CAT, GPX,GR, Alb and TP levels. [40]
42	Di Pierro et al. (2009)- GreenSelect Phytosome	100 obese subjects (both male and female) were divided into 2 groups of 50 each. Group 1 was given hypocaloric diet with green tea phytosome. Group 2 was given only hypocaloric diet. After 90 days, parameters like weight, BMI, LDL, HD, total cholestrol, triglycerides, insulin, growth factor 1,cortisol were determined.	All parameters improved in both groups but there was more weight loss in green tea phytosome group than in diet only group (14 kg loss versus 5 kg loss). Also, no adverse Effects were Reported during and after trial. [41]
43	Scientists at Indena.- Leucoselect phytosome	A double-blind cross-over parallel study in which 24 type 2 diabetes patients were given leucoselect phytosome and control group was given placebo for 4 weeks. Excretion of 8-epi-PGF2□in urine.	Urinary excretion of 8-epi-PGF2□was reduced, indicating improvement in oxidative stress condition in diabetics. [29]

CONCLUSION

In recent times the emerging technology of drug delivery is also being applied to phytopharmaceuticals. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when complexed with phospholipids like phosphati-dylcholine give rise to a new drug delivery system called phytosome showing much better absorption profile following oral administration owing to improved lipid solubility which enables them to cross the biological membrane, resulting better bioavailability i.e. more amount of active principle in the systemic circulation. This means more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney etc) at similar or less dose as compared to the conventional plant extract. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered in this way exhibiting remarkable therapeutic efficacy in animal as well as in human models. Thorough study of literature reveals that several plant extracts (crude, partially purified or fractionated) are reported to possess different significant pharmacological or health promoting properties. These extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential to be used rationally. In this way after screening and selection of potential extracts or constituents from plants, phytosomes can be developed for different therapeutic purposes like cardiovascular, anti-inflammatory, immunomodulator, anticancer, antidiabetic etc or for prophylactic purposes as nutraceuticals, in due course.

REFERENCES

[1] S. Bhattacharya, *Pharma Times*, **2009**, 41,3, 9-12.
[2] A. Joshi, S. Chaturvedi, V. Kumar, A. Pathak, *The Pharma Review*, **2007-08,**127-131
[3] C. Manach, A. Scalbert, C. *Am. J. Clin. Nutr*., **2004,** 79,727-47
[4] E. Bombardelli, S.B. Curri, R.L. Della, N. P.Del, A. Tubaro, P. Gariboldi, *Fitoterapia*; **1989,** 60, 1-9
[5] B. Gabetta, G.F. Zini, G. Pifferi, *Planta Med*. **1989**, 55, 615.
[6] N. Barzaghi, F. Crema,G. Gatti,G. Pifferi, E. Perucca, *Eur.J. Drug Metab. Pharmacokinet.* **1990,** 15, 333-38
[7] S. Malandrino, G. Pifferi, *Drugs Future*; **1990**, 15, 226-227.
[8] A. Comoglio, G. Leonarduzzi, R. Carini, D. Busolin, H. Basaga, E. Alabano, Tomasi, G. Poli, P. Morazzoni, M.J. Magistretti, *Free Radic. Res. Commun.* **1990,** 11, 109-15.
[9] R. Orlando, A. Fragasso, M. Lampertico, *Med Sci Res,* **1990**, 18, 861-863.
[10] C. Marena, M. Lampertico, *Planta Med.* **1991**, 57, 124- 25.
[11] E. Bombardelli, M. Spelta, R. L. Della, S. Sosa, A. Tubaro, *Fitoterapia*, **1991,** 62, 2, 115-22.
[12] G. Pifferi, *Planta Medica*, **1991**, 57, 2, A12.
[13] R. Orlando, A. Fragasso, M. Lampertico, *Med Sci Res,* **1991**,19,827-828.
[14] P. Morazzoni, M.J. Magistretti, C. Giachetti, G. Zanolo, *Eur. J. Drug Metab. Pharmacokinet.*, **1992**, 17, 39-44
[15] R. Carini, A. Comoglio, E. Albano, G. Poli, *Biochem Pharmacol*., **1992**, 43, 2111-15.
[16] M. Conti, S. Malandrino, M.J., *Jpn. J. Pharmacol*. **1992**, 60, 315-21
[17] R. Marcelli, P. Bizzoni, D. Conte, *Eur Bull Drug Res*, **1992**,1, 131-135.
[18] R. Schandalik, G. Gatti, E. Perucca, *Arzneimittelforschung*, **1992**, 42, 964-968.

[19] G. Buzzelli, S. Moscarella, A. Giusti, A. Duchini, C. Marena, M. Lampertico, *Int. J. Clin. Pharmacol. Ther. Toxicol*. **1993**, 31, 456-60.
[20] A. Vailati, L. Aristia, E. Sozze, F. Milan, V. Inglese, P. Calenda, P.A. Bosollo, *Fitoterapia*. **1993**, 64, 219-228.
[21] S. Moscarella, A. Giusti, F. Marra, C. Marena, M. Lampertico, P. Relli, P. Gentilini, G. Buzzelli, *Curr. Ther. Res*., **1993**, 53, 98-102.
[22] P. Morazzoni, A. Montalbetti, S. Malandrino G. Pifferi, *Eur. J. Drug Metab. Pharmacokinet.* **1993**, 18, 289-97.
[23] B. Schwitters, J. Masquelier, *Alfa Omega*, Rome, Italy, **1993**.
[24] R.M. Facina, *Arzneim Forsch*, **1994**, 44, 592-601.
[25] A. Comoglio, A. Tomasi, S. Malandrino, G. Poli, E. Albano, *Biochem Pharmacol*. **1995,** 50, 1313-16.
[26] S.L. Nuttall, M.J. Kendall, E. Bombardelli, P. Morazzoni, *J Clin Pharm Ther.*, **1998**, 23,5, 385-9.
[27] P. Pietta, P. Simonetti, C. Gardana, A. Brusamolino, P. Morazzoni, E. Bombardelli, *Biochem Mol Biol Int*.,**1998**, 46, 5, 895-903.
[28] L. La. Grange, M. Wang, R. Watkins, D. Ortiz, M.E. Sanchez, J. Konst, C. Lee, E. Reyes, *J. Ethnopharm*. **1999**, 65, 53-61.
[29] www.indena.com
[30] Y.N. Jiang, Z.P. Yu, Z.M. Yan, J.M. Chen, *Zhongguo Zhong Yao Za Zhi,*. **2001**, 26, 2, 105-8.
[31] Y. N. Jiang, H. Y. Mo, J.M. Chen, *Zhongguo Zhong Yao Za Zhi*, **2002**, 27, 3, 221-4.
[32] A. Busby, L. La Grange, J. Edwards, J. Kings, *J Herb Pharmacother.*, **2002**, 2, 1, 39-47.
[33] G.B. Vigna, F. Costantini, G. Aldini, M. Carini, A. Catapano, F. Schena, A. Tangerini, R. Zanca, E. Bombardelli, P. Morazzoni, A. Mezzetti, R. Fellin, R. M. Facino, *Metabolism*, **2003**,52, 10, 1250-7.
[34] D. Tedesco, S. Steidler, S. Galletti, M. Tameni, O. Sonzogni L. Ravarotto, *Poultry Sci.*, **2004**, 83, 11,1839-43
[35] K. Maiti, K. Mukherjee, A. Gantait, H.N. Ahamed, B.P. Saha, P.K. Mukherjee, *Iran J. Pharmacol. Ther*, **2005**, 4, 84-90.
[36] X. Yanyu, S. Yunmei, C. Zhipeng, P. Quineng, *Int J Pharm*., **2006**, 3, 307, 1,77-82.
[37] K. Maiti, K. Mukherjee, A. Gantait, B.P. Saha, P.K. Mukherjee, *Int. J. Pharm*.,Sept. **2006**.
[38] K. Maiti, K. Mukherjee, A. Gantait, B.P. Saha, P.K. Mukherjee, *J Pharm Pharmacol*, 58, 9, 227-233.
[39] S.R. Naik, V.W. Pilgaonkar, V.S. Panda, *Phytother Res*., **2006,** 20, 11, 1013-6.
[40] S.R. Naik, V.S. Panda, *Fitoterapia*, **2008**, 79, 6, 439-45.
[41] F. D. Pierro, A. B. Menghi, A. Barreca, M. Lucarelli, A. Calandrelli, *Altern Med Rev*., **2009**, 14, 2, 154-60.