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Examining the potential therapeutic Value of Curcumin, Piperine & Gingerol Novel Formulation

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KEYWORDS

Curcumin; Piperine; Gingerol; Polyherbal formulation; Novel drug delivery system; Herbal medicine; Antioxidant activity; Anti-inflammatory activity; Anticancer activity; Immunomodulatory effect; Wound healing.

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Abstract

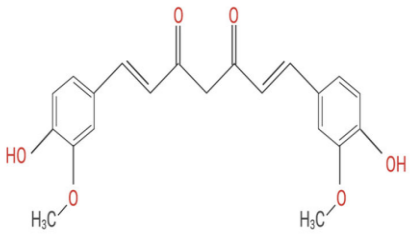
This review focuses on the potential of curcumin, piperine and gingerol. Curcumin has its wound healing, anti-cancer, diabetes, arthritis, anti-oxidant properties. Piperine shows effect such as antioxidant, anti-inflammatory, anticancer, hepatoprotective, antidiarrheal, antidepressant, analgesic and Gingerol shows effect such as antioxidant, anti-inflammatory and anti-cancer. The combination of Curcumin, Piperine and Gingerol used to provides immunity, protect against illness and promote general wellbeing. According to review there is no novel formulation available for this combination. So, we can make various novel formulations to increase its positive effects. In this review we have proposed various analytical methods to identify and quantify Curcumin, Piperine and Gingerol from their form.

1 Introduction:

1.1 Curcumin:

Turmeric is a spice which has received great interest from the medical worlds as well as culinary world. Turmeric is a rhizomatous (Turmeric) perennial herbaceous plant that belongs to the ginger family. The medicinal properties of turmeric, the source of curcumin, have been known for thousands of years; however, the ability to determine the exact mechanism of action and to determine the bioactive components have only recently been investigated. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-

heptadiene-3,5-dione), also called diferuloylmethane, is the main natural



polyphenol found in the rhizome of Curcuma longa (turmeric) and in others Curcuma spp[1].

Figure 1 Structure of Curcumin

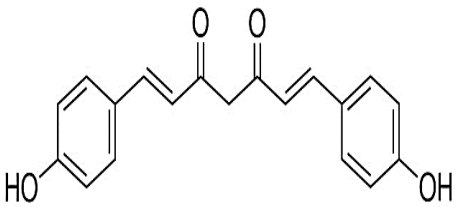
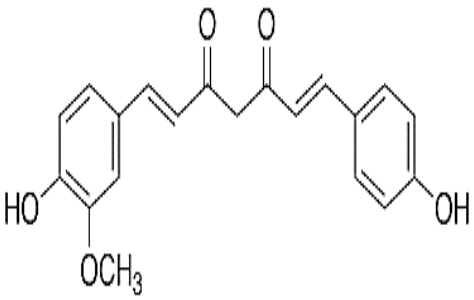


Figure 2 Structure of



Bisdemethoxycurcumin

Figure 3 Structure of Demethoxycurcumin

Curcumin, a polyphenol, has been shown to target multiple signalling molecules while also demonstrating activity at the cellular level, which has helped to support its multiple health benefit [1]. Curcuma has a purifying effect on blood, and supports the work of the pancreas and liver. Research is ongoing on the use of these substances in the prevention and treatment of diseases such as rheumatoid arthritis, diabetes, and Alzheimer's disease. In folk medicine turmeric is used, among others in the treatment of diseases of the gall bladder, kidneys and also in stomach ailments because of the fact that it supports metabolism and accelerates digestion. Various species of the Curcuma genus have been known in medicine since at least the 19th century [5].

Turmeric root have within their composition, among others: mineral salts (lime, iron, magnesium), fats, fiber, proteins, starch and essential oils. The Curcuma rhizome has an intense yellow colour, derived from dyes, the so-called curcuminoids, which include compounds such as curcumin (diferuloylmethane, makes up about 70%), demethoxycurcumin (about 15%) and bis-dimethoxycurcumin (about 3%). The Figure 3 below shows Curcuma powder [5].

1.1.1 Pharmacological Actions of Curcumin:

Although curcumin was isolated in the 19th century, its pharmacological activities and medicinal application have been known since the Vedic ages. Curcumin is effective against various chronic diseases, which are discussed below [6].

1.1.1.1 Curcumin in Wound Healing:

Wound healing consists of an orderly progression of events that include inflammation, granulation and tissue remodelling. During wound healing, the migration of various cells represents potential contact with growth factors required for the regulation of biological processes. TGF-β-1 is an important factor in wound healing as it stimulates the expression of fibronectin and collagen in fibroblasts and increases the rate of granulation. Curcumin modulates TGF-β-1 activity, encourages the formation of new skin (re-epithelialization) and also enhances a signal to the immune system that recruits macrophages to "recycle" dead tissue. A preclinical study of topical curcumin was conducted in a dexamethasone-impaired cutaneous rat model of wound healing. Curcumin significantly accelerated wound healing with or without dexamethasone treatment by enhanced expression of TGF-β-1 and TGF-β receptor type-2 (TGFR-2). The levels of iNOS were increased following curcumin treatment in unimpaired wounds, but not in Dexamethasone Impurity wounds, indicating that topical curcumin enhanced the dexamethasone-impaired wound repair along with differential regulatory effects on TGF-β-1, TGF receptors and iNOS in this model of cutaneous wound healing. Curcumin-treated wounds were found to heal much faster, as indicated by improved rates of epithelialization and wound contraction. Curcumin decreased the levels of lipid peroxides while significantly increasing the levels of superoxide dismutase, catalase and glutathione peroxidase, thereby exhibiting antioxidant properties to accelerate wound healing. These findings indicate that curcumin indeed possesses the potential to inhibit H2O2 damage in human keratinocytes and fibroblasts, which may enhance wound healing [6].

1.1.1.2 Curcumin in Cancer:

Since ancient times, curcumin has been known for its anti-inflammatory, antioxidant and anticarcinogenic properties. The pleiotropic role of this dietary compound includes the modulation of several molecular targets at multiple levels, which enhances its antiproliferative properties in a wide variety of cancer cells. Several reports have described the therapeutic activity of curcumin in gastrointestinal cancers, such as

esophageal, gastric, intestinal, pancreatic and colorectal cancer. It was found to inhibit the cytokine-induced activation of inducible nitric oxide synthase (iNOS), MAPK, vascular cell adhesion protein (VCAM), β-catenin, COX-2, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), matrix metalloproteinases (MMPs), Ca2+ mobilization, Bcl2-L-1 and phosphorylated STAT3. In addition, curcumin activates caspase-3 and caspase-8 and induces PARP cleavage in the previously mentioned gastrointestinal cancers. Curcumin blocks tumour initiation and promotion and suppresses the growth of various cancer cells, including B-cell and T-cell leukaemia, colon and breast carcinoma and multiple myeloma. In human head and neck squamous carcinoma cells curcumin was found to block NF-κB signalling and IKK activation, suppressing various cellular proliferative and survival genes (e.g., those encoding Bcl-2, G1 /S-specific cyclin-D1 (BCL-1), IL-6, COX-2 and MMP-9), caspase activation and PARP cleavage. Apart from causing tumour cell death, curcumin was also found to stop the invasion and metastasis of cancer cells. It was reported to inhibit COX-2 upregulation, MMP-9 overexpression and phorbol ester-induced metastasis by blocking ERK-1/ERK-2 phosphorylation and NF-κB transcriptional activity in MCF-10A human breast epithelial cells [6].

1.1.1.3 Curcumin in Diabetes:

Several studies have shown that curcumin has the ability to lower blood glucose levels by increasing the activity of an enzyme that plays a key role in blunting the blood sugar rise that follows meals and produces insulin. A pharmacokinetic study of curcumin was conducted in diabetic albino rats. In this model, it reduced blood sugar, as well as haemoglobin, glycosylated haemoglobin, oxidative stress (as demonstrated by lower levels of Thio barbituric acid-reactive substances) and the enzymatic activity of sorbitol dehydrogenase, which catalyses the conversion of sorbitol to fructose. Furthermore, curcumin controls the symptoms associated with type 2 diabetes, a disorder associated with a failure to use insulin properly. Several studies have linked inflammation and obesity to the development of type 2 diabetes. Curcumin was reported to control diabetes in high fat diet-induced obesity and leptin-deficient ob/ob male C57BL/6J mice. It reduced macrophage infiltration, hepatic NF-κB activity and markers of hepatic inflammation, and increased adiponectin production in adipose tissue. These results suggest that curcumin potentially controls the inflammatory and metabolic

derangements associated with obesity and that it improves glycaemic control in mouse models of type 2 diabetes. Furthermore, curcumin lowered the cholesterol and phospholipid levels in streptozotocin induced diabetic animals. Curcumin's ability to lower blood glucose and cholesterol and antioxidant and free radical-scavenging properties make it a potential therapeutic for the treatment of diabetes [6].

1.1.1.4 Curcumin in Arthritis:

Arthritis is a chronic disease characterized by inflammation of the joints. Curcumin has been reported to suppress proinflammatory cytokines (e.g., TNF and IL-1), proinflammatory enzymes (e.g., COX2, LOX) and MMPs and blocks the NF-κB signalling pathway. In a 2-week, short-term, double-blind, crossover study, the antirheumatic activity of curcumin (1200 mg/day) was compared with that of phenylbutazone (300 mg/day) in 18 patients with rheumatoid arthritis. There were remarkable improvements in morning stiffness, walking time and joint swelling. In a similar trial in which the number of patients was increased to 31 and the dose level was increased to 1800-2100 mg/day for longer periods of time (5-6 weeks), significant improvements were observed in all patients. The cartilage degeneration in arthritis is believed to be initiated by IL-1. Curcumin inhibits IL-1, MAPK, AP-1 and NF-κB and downregulates the expression of genes encoding MMPs in particular chondrocytes. In human chondrocytes, it repressed MMP-3 expression by 48- 99% and MMP-13 expression by 45-97%, whereas these values were 8-100% and 32-100%, respectively, in bovine chondrocytes. Curcumin's ability to inhibit inflammatory signal transduction could be useful for suppression of the symptoms associated with arthritis [6].

1.2 Piperine:

Piperine is a compound belonging to the alkaloids; it is responsible for the pungent taste of various pepper species, and has, in addition to being found in the members of the Piperaceae family, been detected in several other plant species (Rhododendron faurie, Vicoa indica, Anethum sowa, and others). Black pepper (Piper nigrum L.) is the most used among the pepper species, and along with its worldwide utilization as a spice, it is known as an important medicinal plant [7].

Pepper is traditionally recommended for fevers and a variety of gastrointestinal conditions, as well as for neurological and broncho-pulmonary disorders (asthma and chronic bronchitis). Investigations on piperine bioactivities have reported the very high spectrum of physiological effects, including antihypertensive, antiaggregant, antioxidant, antitumor, antispasmodic, anti-

asthmatic, antidepressant, anxiolytic, and many others [7].

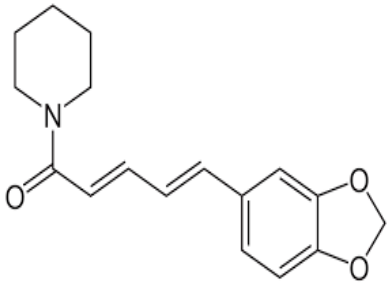


Figure 4 Structure of Piperine

1.2.1 Pharmacological Actions of Piperine:

1.2.1.1 Antioxidant activity:

It is well-known that various spices and herbs, including a black piper, contain numerous active ingredients, like flavonoids, terpenoids, phytoestrogens and minerals. Among them, piperine was detected to have an antioxidant potential, which might diminish oxidative stress in the cells caused by the high-fat diet. Moreover, piperine was also shown to decrease the level of the Thio barbituric acid reactive substances via the maintenance of catalase, glutathione, glutathione peroxidase, Glutathione-S transferase, and superoxide dismutase concentrations. This substance could also improve the activity of biotransformation enzymes in the liver in a dose-dependent way. Furthermore, several studies on the antioxidant activity of piperine have been conducted to establish the reduction of lung metastatic incidence in the B16F-10 melanoma cells through the alteration in lipid peroxidation and the stimulation of antioxidant enzymes [11].

1.2.1.2 Anti-inflammatory activity:

Various anti-inflammatory effects of substances extracted from plants are known for many therapeutic applications in modern medicine and pharmacy to treat different disease. In particular, some ethanolic and hexane extracts of black pepper have exposed a significant anti-inflammatory activity in mice and rats, using different dosage protocols. Moreover, piperine had also revealed the same activity in the interleukin (IL) 1b-activated fibroblast-like synoviocytes, inhibiting the LPS-stimulated endotoxins. Further, piperine might be viewed as a potent immunomodulator, inhibiting airway inflammation a murine model of asthma by the enhanced expression of TGF-beta gene in the lungs. Piperine was also detected to reduce the production of IL-6, MMP-13, and prostaglandin E at the concentration range of 10e100 mg/ml. In another study, piperine was co-administered with curcumin from Curcuma longa to suppress a high fat diet induced inflammation in the C57BL/6 mice and for the prevention of metabolic syndrome. Apart from that, the piperine anti-inflammatory potential had been investigated at colorectal sites, inhibiting the FFA-induced TLR4 mediated inflammation and acetic acid-induced

ulcerative colitis in mice. Finally, this compound was evaluated in the carrageenan-induced inflammation assay in mice to assess the analgesic and anti-inflammatory activities of piperine activities at the oral dose of 6 mg/kg/day [11].

1.2.1.3 Anti-cancer and hepatoprotective activity:

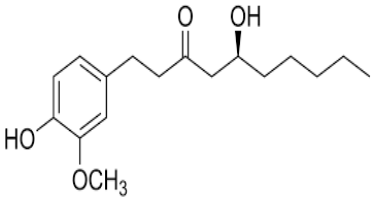
The antitumor activity of piperine has been detected after its oral administration to reduce the incidence of some forms of gastrointestinal cancers. An alcoholic extract of black pepper, containing piperine, was found to be effective against lung cancer via altering lipid peroxidation, which leads to the spread of free radical reactions and cellular damage. Besides, piperine might restrict the cell cycle at G1/S phase, inhibiting the HUVECs (human umbilical vein endothelial cells) proliferation and migration. In animal models, piperine can hinder angiogenesis, suppressing the tubule formation by endothelial cells and the phosphorylation of protein kinase B. Some anti-cancer activity of piperine can be seen by applying it in the combination with the FDA-approved antineoplastic compound docetaxel to treat castrate-resistant prostate cancer. By restricting the enzymatic activity of hepatic CYP3A4, piperine decreases the metabolizing rate of this drug in the liver. Additionally, it has also been studied that the application of piperine in a nutritional supplement might also enhance the docetaxel immunosuppressive effects in xenograft animal models without severe side-effects. Piperine was also found to be active against both androgen-dependent and independent prostate cancer cell lines (LNCaP, 22RV1, PC-3, and DU145), inducing apoptosis through the activation of PARP-1 and caspase-3 proteins. In the LNCaP prostate cancer cells, piperine disrupts the androgen receptor expression, significantly reducing the detection of the prostate-specific antigen. It was previously established that the methanolic extract of black pepper has the hepatoprotective properties confirmed in Wistar rats with induced hepatic damage caused by ethanol-CCl4. In these experiments, ethanol-CCl4 was administered to increase the levels of triglycerides, alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin. All these parameters came to normal after the animals were treated with the methanolic extract of black pepper. This extract reduced the lipid peroxidation as a hepatoprotective effect at the administered doses alone or in combination with some antituberculosis drugs. In another study, the D-galactosamine-induced liver injury modelled in mice was treated with piperine to normalize the concentration of glutamic oxaloacetic transaminase and pyruvic transaminase levels in serum. The proposed

mechanism had been found to be associated with the reduced sensitivity of hepatocytes to TNF-a[11].

1.3 Gingerol:

Gingerol (5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone) is a water hating yellowish to buff colour poly phenolic constituent, obtained from Zingiber officinale (Zingiberaceae). It has analgesic, hypoglycemic, hepatoprotective, immune stimulant, anti-inflammatory, antibacterial, antimicrobial, antifungal, antiviral, antiparasitic, antitrypanosomally, antidermatophytic, antioxidant, antifertility, tuberculostatic and anticancer properties [13].

The oil contained in the Ginger rhizome positively affects digestive work, which may be helpful in digestive disorders, food poisoning or indigestion, because it exhibits



choleretic and diastolic effects and may be helpful in stimulating gastric juices. In addition, Ginger is known for the relief of nausea and antiemetic (Zingiberis rhizoma) [5].

Figure 5 Structure of Gingerol

1.3.1 Pharmacological Actions of Gingerol:

1.3.1.1 Antioxidant Activity:

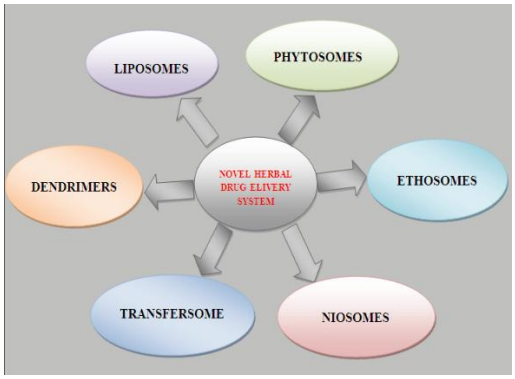
Z. officinale is effective in Parkinson's disease because zingerone, an active ingredient in ginger scavenged peroxide and hydroxyl ions as well as suppress lipid peroxidation. Ginger consists with reno-protective effect in renal failures because of anti-inflammatory properties by attenuating serum C-reactive protein levels and antioxidant effects by reducing lipid peroxidase marker, malondialdehyde levels and increasing renal superoxide dismutase activity [15].

As a natural antioxidant, 6-gingerol is recommended for the prevention of many diseases. The antioxidant properties of the phenolic compound may be related to its ability to donate electrons and to act as a free radical scavenger by the formation of a stable phenoxyl radical. In this study, myofibroblast differentiation, collagen production, and phosphorylation of Smad2/3 were also prevented by 6-gingerol. These results suggested that 6-gingerol may have some antioxidant effect in inhibiting the production of the extracellular matrix in the development of nasal polyps. β-Amyloid (Aβ) is a typical neuropathological marker for Alzheimer's disease (AD) and has been reported to cause apoptosis in neurons via oxidative and/or nitrosative stress. 6-Gingerol pre-treatment

prevented Aβ-induced cytotoxicity and apoptotic cell death. For the mechanism, 6-gingerol effectively decreased the level of reactive oxygen and/or nitrogen species and restored antioxidant glutathione levels [16].

1.3.1.2 Anti-inflammatory effect:

Ginger is well known for its therapeutic use in inflammatory disorders, and 6-gingerol is one of the active ingredients responsible for these properties. The cytokines tumor necrosis factor, TNF-α, and interleukin (IL)-1β are thought of as alarm cytokines to initiate inflammatory cell recruitment by stimulating the expression of pro-inflammatory genes. Furthermore, mitogen-activated protein kinase phosphatase-5 (MKP5) has a role in mediating the anti-inflammatory activities. It was reported that TNF-α and IL-1β can increase p38-dependent nuclear factor kappa-β (NFkβ) activation and expression of the pro-inflammatory genes cyclooxygenase-2 (COX-2), IL-6 and IL-8 in normal prostatic epithelial cells. 6Gingerol can up-regulate MKP5, and decrease cytokine-induced p38-dependent pro-inflammatory changes [16].



1.3.1.3 Immuno-modulatory activity:

The beneficial effects of ginger in treating coughs, colds and flu is probably linked to immune-boosting properties of the plant. However, researchers have evaluated the role of gingerols as an immunosuppressant in a quest to find therapeutic agents for treating auto-immune diseases [43].

2 Novel Formulation Of Curcumin, Piperine And Gingerol:

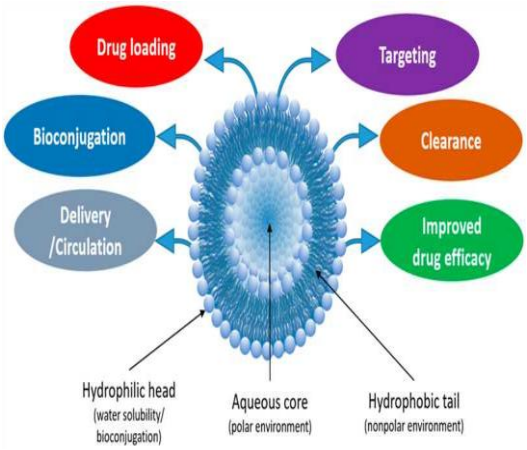
Definition of Novel Formulation: means any new, novel or proposed formulation which: (a) is different than the Existing Formulation; and (b) results from the activities conducted under this Agreement by PARI or ABARIS, individually or jointly with one another or third parties [17].

Figure 6 Novel Herbal Drug Delivery System[18]

2.1 Curcumin:

2.1.1 Liposomes:

CUR has exerted therapeutic effects in many types of cancer including lung, cervical, prostate, breast, osteosarcoma (OS) and liver cancers. However, in vivo activities of CUR are limited due to its poor solubility and low bioavailability.



Liposomes provide a type of effective drug delivery system for CUR. As we discussed in this review, liposomes could enhance antitumor and pharmacological activities of CUR by improving pharmacokinetics and pharmacodynamics and reduce the dosage required for targeting tumour [19].

Figure 7 Structural features of liposome

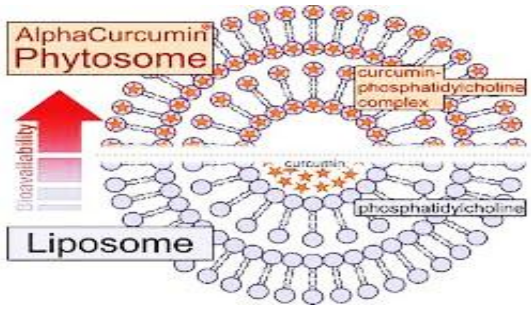
Advantages of liposome formulation:[21]

- Hydrophobic and hydrophilic drug can be delivered.
- Liposome herbal therapy acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as
- Sustained and controlled release of formulation can be possible.

Liposomes evolved into an important tool in pharmaceutical drug delivery. Their unique structure of vesicular phospholipid membranes offers the opportunity to formulate both hydrophilic drugs in their inner aqueous cavity and hydrophobic drugs in their phospholipid bilayer. Hence, liposomes can be advantageous to improve the solubility of poorly soluble drugs as well as to protect drugs from degradation or metabolic processes. Furthermore, liposomes are often applied as circulating drug depots. This can be particularly beneficial in the delivery of cytostatic, as nanocarriers are supposed to accumulate in solid tumours due to the enhanced permeability and retention effect [22].

2.1.2 Phytosomes:

Curcumin, a hydrophobic polyphenol, is the principal constituent extracted from dried rhizomes of Curcuma longa L. (turmeric). Curcumin is known as a strong anti-oxidant and anti-inflammatory agent that has different pharmacological effects. In addition, several studies have demonstrated



that curcumin is safe even at dosages as high as 8 g per day; however, instability at physiological pH, low solubility in water and rapid metabolism results in a low oral bioavailability of curcumin. The phytosomal formulation of curcumin (a complex of curcumin with phosphatidylcholine) has been shown to improve curcumin bioavailability. This review focuses on the pharmacokinetics as well as pharmacological and clinical effects of phytosomal curcumin [23].

Figure 8 Phytosomal Curcumin Complex [24]

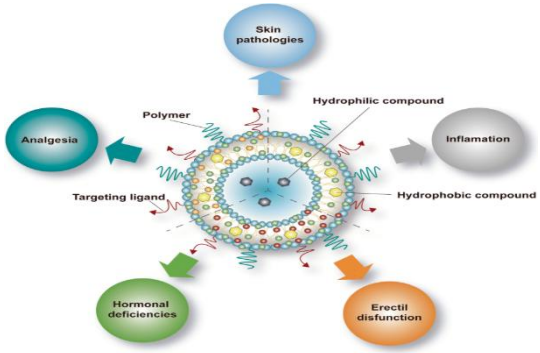
Phytosomes have the following advantages:[21]

- Improve the absorption of lipid insoluble polar phytoconstituents, enhance the bioavailability.
- Appreciable drug entrapment which becomes very beneficial.
- Reduce the dose due to increased absorption.
- Phosphatidylcholine shows synergistic effect because it is a hepatoprotective also.

2.1.3 Ethosomes:

Many studies have confirmed CUR as a unique Phyto-drug that can be used for the treatment of melanoma. Some of these reports have utilized various innovative drug delivery systems of CUR and its analogues in melanoma therapy. The available literature reports only a few studies, where CUR has been delivered transdermal using ethosomes as carrier systems. However, the applicability of CUR loaded ethosomes as innovative drug delivery carriers for the treatment of melanoma has so far not been reported. Thus, the present study aimed to develop, optimize and characterize an ethosome formulation of CUR for melanoma targeting by using a 3^2-factorial design [25].

Ethosomes are the vesicular systems which contain lipid bilayer just like conventional vesicles but they contain ethanol in higher concentration in place of cholesterol. Ethanol is a well-known skin penetration enhancer. It increases the drug penetration into the skin by reduction in the barrier property of stratum corneum. Most of



common inflammatory skin disorders desire that the drug should be delivered to the deeper skin layers where inflammation occurs. Poor absorption, quick metabolism and less solubility in water are the main reasons for the low bioavailability of curcumin. To overcome these problems, our investigation focuses on formulation and optimisation of curcumin ethosomes for transdermal delivery [26].

Figure 9 Ethosomes as Nanocarriers for the Development of Skin Delivery Formulations [27]

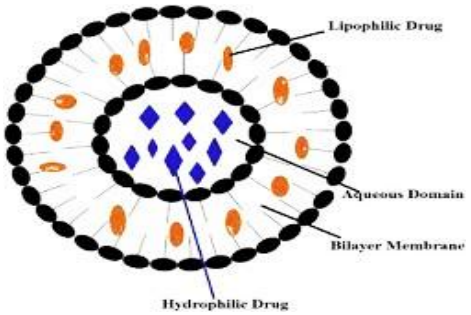
Advantages of ethosomal drug delivery:[21]

- Transdermal permeation of drug through skin can be enhanced.
- Large amounts of diverse groups of drugs can be delivered.
- The ethosomal drug is administered in semisolid form, resulting in improved patient compliance.

2.1.4 Niosomes:

Surfactant-based colloidal drug carriers like niosomes have been considered as an efficient formulation to transfer higher amounts of drugs through the skin and could be released at the controlled rates for a systemic absorption. Niosomes are commonly nontoxic with low production cost and have suitable stability for a longer duration. Niosomes containing curcumin could be used as a platform for prolonged topical delivery to the skin and thus enhancing the anti-inflammatory effect of the drug. The topical delivery of certain drugs using niosome has also been developed and There are other studies where researchers have used different techniques to make various curcumin niosomes using various surfactants to improve transdermal delivery of curcumin[28].

In this study, a novel curcumin-loaded niosomes system was developed to effectively deliver curcumin for the treatment of ovarian cancer. It was demonstrated that niosomes provided a biochemically stable protection and high



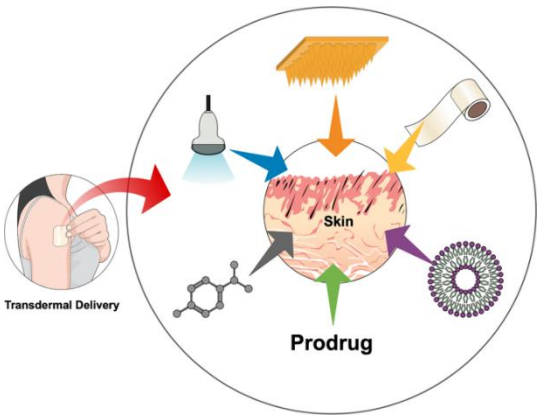
entrapment efficiency of curcumin. Moreover, curcumin-niosomes exhibited enhanced cellular uptake, cytotoxic activity, cell cycle arrest, and apoptotic rate against ovarian cancer A2780 cells. Taken together, curcumin-niosomes are potential delivery formulations for the treatment of ovarian cancer[29].

Figure 10 Structure of Niosome [30]

Niosomes are different from liposomes in that they offer certain advantages over liposomes. Liposomes face problems such as they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Niosomes do not have any of these problems [21].

2.1.5 Transdermal Drug Delivery System

The drugs of ayurvedic origin can be utilized in a better form with enhanced



efficacy by incorporating in modern dosage forms. Transdermal film formulations of CUR, a well-known phytoconstituent, were prepared for improving its anti-inflammatory activity. Transdermal film of CUR showed best in vitro skin permeation and anti-inflammatory activity as compared to other film formulations. The CUR transdermal films developed in this study have great utility and are a viable option for effective and controlled management of inflammation [35].

Figure 11 Transdermal drug delivery systems [36]

2.2 Piperine:

2.2.1 Liposomes:

The encapsulation of drug into vesicular delivery systems has been widely used to enhance the solubility, stability, therapeutic efficacy and bioavailability of poorly soluble drugs. Liposomes are widely used as a delivery system for hydrophilic and hydrophobic drugs. Liposomes contain a lipid bilayer that is similar to the cell membrane. They are composed of phospholipids, cholesterol and surfactant. Liposomes are considered nontoxic, biodegradable and modulate the release properties. However, liposomes can show instability when given orally due to chemical and enzymatic degradation. Therefore, chitosan (C) coating is performed over the surface of the liposomes to modify the surface, leading to better liposomal characteristics. It forms a surface coat over the liposomes by the electrostatic deposition method, creating a positively charged chitosan–liposome complex. Liposomes and chitosan-coated liposomes to compare physicochemical parameters. Finally, the selected chitosan-coated PPN liposomes were evaluated for cytotoxic effects in the MF7 breast cancer cell line [38].

2.2.2 Phytosome:

Phytosomes are nano-size carriers, providing new opportunities to enhance bioavailability of drugs. The interaction between natural ingredients and phospholipids can be used for therapeutic fortification. Phytosomal drug delivery systems have superior functionalities (monodisperse, more surface area, small size) than conventional dosage forms. Unlike liposomes and lipid emulsions, the phytoconstituents are part of the vesicular membrane of phytosome, thus help phytocomponents to pass through the cell membranes and reach the target site or receptor. This property makes them attractive carriers for active pharmaceutical ingredients in comparison with the conventional counterparts. Moreover, the bioavailability of many herbal extracts has been improved through phytosomal carriers. The presence of phospholipids in phytosomes makes them an ideal candidate to carry hydrophilic as well as lipophilic drugs. The cell-membrane-like composition of phospholipid molecules helps them to permeate through physiological cell membranes easily. Hence, Phytosomes can appropriately decrease absorption and bioavailability related issues of drugs. Likewise, in the case of domperidone (DPD), phytosomes might facilitate the absorption and permeation through the membranes of intestinal epithelial cells [39].

2.2.3 Nanoparticles:

Novel drug delivery system is a unique method to delivery drug that formulate of herbal nanoparticles of piperine this novel formulation increases the activity and efficiency of piperine. The nanoparticles prepared from long pepper fruit Extract, PVA solution 0.2% and Dichloromethane by using simple solvent evaporation method and also other preparation method of nanoparticles. This nanoparticles form improves various activity such as antimicrobial, Antifungal, Antioxidant, Hepatoprotective activity and Bioavailability of piperine. The observation found to be in vitro dissolution parameter release pattern of piperine high as compared to simple long pepper fruit Extract. Herbal nanoparticles are less side effect and less adverse effect. It is simple idea behind the novel drug delivery system in natural medicines. Modern phytopharmaceutical research can solve the scientific needs (such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) of herbal medicines to be incorporated in novel drug delivery system [40].

2.3 Gingerol:

2.3.1 Liposome:

Making chemotherapy drugs targeted and drug delivery to the areas whose access is restricted are among the strategies that can be used to reduce the side effects of

chemotherapy drugs. Previous studies have shown that nanoparticles can be used as inconclusive tools for drug delivery to tumours. Major breast diseases treated by combinations of nanoparticles and anticancer drugs in animal models indicate this fact [41].

Gingerol is one of the drugs used to treat breast cancer. For passage through biological barriers, drug protection, and release of optimal dosages, nanoscale injectable drug-carriers are used. Liposome is one of these carriers. Recent advances in nanotechnology allow targeted treatment of animal and human diseases while reducing medication side effects [41].

Liposomes are vesicles composed of one or more concentric phospholipid layers surrounding aqueous chambers. Liposomes protect drugs from degradation while minimizing their side effects. This study aimed to nano liposomal gingerol to improve its therapeutic index and reduce its side effects [41].

2.3.2 Phytosome:

Phytosome is protected process created by Indena, to fuse phospholipids into standardized concentrates thus immeasurably enhance their ingestion and usage. The expression "Phyto" implies plant while "somes" implies cell-like. The phytosome structure is a little cell in itself, as the profitable segments of the home-grown concentrate are shielded from devastation by the stomach related emissions and gut microorganisms. Water soluble phytoconstituents can be reformed over into lipid-perfect atomic complex and in this way are suitably called phytosome [42].

Phytosome process, connected to numerous prevalent home-grown concentrates, including phytoconstituents, drives these particles for direct binding to phosphatidylcholine, which implies that the choline ties to phytoconstituents while the fat-dissolvable phosphatidyl divide containing the body and tail then envelopes the choline-bound material. The outcome is a little microsphere or cell. The phytosome procedure has been connected to numerous prominent home-grown concentrates including Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea and ginseng [42].

3 Conclusion:

The detailed review of this topic shows that curcumin gives pharmacological effect in some disease such as wound healing, cancer, diabetes, arthritis, HIV etc. Piperine shows effect such as antioxidant, anti-inflammatory, anticancer, hepatoprotective, antidiarrheal, antidepressant, analgesic and Gingerol shows effect such as antioxidant, anti-inflammatory and anti-cancer. As per literature article by combining of these three

drugs it shows pharmacological effects such as provides immunity, protect against illness and promote general wellbeing. It was also reviewed that there is no such novel formulation of combination of curcumin, piperine, and gingerol. So to increase its bioavailability we can use various novel methods for formulation.

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