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EFFECT OF NOVEL DRUG DELIVERY SYSTEM IN HERBAL MEDICINES FOR INFLAMMATION: A REVIEW

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ABSTRACT

Inflammation is defined as the local response of living mammalian tissues to injury due to any agent and the drugs used to treat inflammation are called anti-inflammatory. The agents which cause inflammation include infective agents, immunological agents, physical agent, chemical agents, inert materials. There is no single test that can diagnose inflammation. Instead based on the symptoms blood tests, serum protein electrophoresis (SPE), C-reactive protein (CRP), ESR, etc. are used. Usually NSAIDs like aspirin, naproxen and steroid injections like corticosteroids are used to treat inflammation. Herbal drugs has been used for the prevention and treatment of various diseases from time immemorial. To increase the safety and efficacy of herbal drugs NDDS can be implemented.

KEYWORDS: Inflammation, NSAIDs, liposome, NDDS, herbal extract.

INTRODUCTION[1,2,3,20,21,23,24,25]

A drug or substance that reduces inflammation (Redness, Swelling and Pain) in the body is called an anti-inflammatory drug. Anti-inflammatory agents block certain substances in the body that cause inflammation and are used to treat many different conditions. Anti-inflammatory is the property of a substance or treatment that reduces inflammation or swelling. Inflammation occurs when infectious micro-organisms like bacteria, virus or fungi, etc. invade the body, reside in particular tissues and /or circulate in the blood. Inflammation also occurs in response to processes such as tissue injury, cell death, cancer, ischemia and degeneration. Both the innate and adaptive immune responses are involved in the formation of inflammation.

Steroidal and non-steroidal anti-inflammatory drugs are currently the most widely used in the treatment of inflammation. NSAIDs are the drugs used to relieve pain, reduce inflammation and fever. They are also used to relieve symptoms of headaches, painful periods, sprains and strains, colds, flu, coronavirus, etc. NSAIDs are available in the form of tablets, capsules, suppositories, creams, gels and injections. Some of the NSAIDs are over the counter drugs. NSAIDs include ibuprofen, naproxen, diclofenac, celecoxib, mefenamic acid, etoricoxib, indomethacin, aspirin, etc. There is a risk of side effects from NSAIDs which include indigestion, dizziness, headaches, stomach ulcers, etc. Some NSAIDs also react unpredictably with other medicines.

Plants have the ability to synthesize a wide variety of phytochemical compound as secondary metabolites which shows anti-inflammatory activity. Medicinal plants and their secondary metabolites are used in the treatment of various diseases. There is a need for safe, potent, non-toxic or less toxic anti-inflammatory drug. Plants are used in traditional medicines to treat chronic and even infectious diseases. The anti-inflammatory effect of various herbs has been evaluated which include Curcuma longa, Zingiber officinale, evening primrose, etc.

Nowadays modern medicines target exactly the affected or diseased area and thereby drug reaches only to that area. Novel drug delivery system (NDDS) is a novel approach to overcome the limitations of the traditional drug delivery system. If the novel drug delivery technology is applied in herbal medicine it increase the efficacy and also reduce the side effects of herbal drugs. NDDS offer advantages like enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery and protection from physical and chemical degradation, increase efficacy and reduce side effects.

Inflammation

Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation, and acts by removing injurious stimuli and initiating the healing process. Inflammation is therefore a defense mechanism that is vital to health. Usually, during acute inflammatory responses, cellular and molecular events and interactions efficiently minimize impending injury or infection. This mitigation process contributes to restoration of tissue homeostasis and resolution of the acute inflammation.

Types of inflammation

There are two types of inflammation depending upon the defense capacity of the host and duration of response.

1. Acute inflammation

It is of short duration (Lasting less than 2 weeks) and represents the early body reaction, resolves quickly and is usually followed by healing. The main features are:

1) Accumulation of fluid and plasma at the affected site
2) Intravascular activation of platelets
3) Polymorphonuclear neutrophils as inflammatory cells.

2. Chronic inflammation

It is of longer duration and occurs either after the causative agent of acute inflammation persists for a long time, or the stimulus is such that it induces chronic inflammation from the beginning.

The characteristic feature of chronic inflammation is presence of chronic inflammatory cells such as lymphocytes, plasma cells and macrophages, granulation tissue formation, and in specific situations as granulomatous inflammation.

Signs of inflammation

The cardinal signs of inflammation are:

1. Rubor (Redness)
2. Tumor (Swelling)
3. Calor (Heat)
4. Dolor (Pain)
5. Function laesa (Loss of function)

Etiology of inflammation[1]

Non-infectious factors

1. Physical: Burn, Frostbite, Physical injury, Foreign bodies, Trauma, Ionizing radiation.
2. Chemical: Glucose, Fatty acids, Toxins, Alcohol, Chemical irritants (Including fluoride, Nickel and Other trace elements).
3. Biological: Damaged cells.
4. Psychological: Excitement.

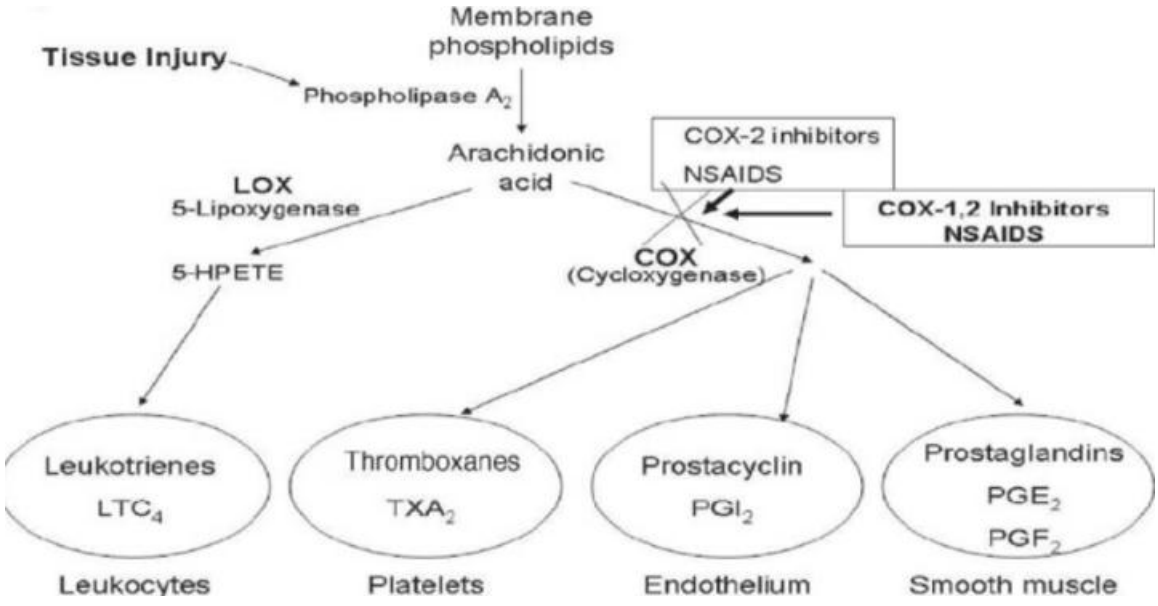
Infectious factors

Bacteria, viruses, other micro-organisms.

Inflammatory response mechanisms[4]

The inflammatory response is the coordinate activation of signalling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood. Inflammation is a common pathogenesis of many chronic diseases, including cardiovascular and bowel diseases, diabetes, arthritis and cancer. Although inflammatory response processes depend on the precise nature of the initial stimulus and its location in the body, they all share a common mechanism, which can be summarized as follows:

1. Cell surface pattern receptors recognise detrimental stimuli
2. Inflammatory pathways are activated
3. Inflammatory markers are released
4. Inflammatory cells are recruited



Schematic representation showing that when a cell membrane is injured the arachidonic acid pathway is activated to initiate the local inflammatory response.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in inflammation[19]

The NSAIDs exhibit anti-inflammatory, analgesic and antipyretic properties. The USFDA approved NSAIDs for OTC analgesic use can be separated into three groups: salicylates, represented by aspirin; propionic acid derivatives, including ibuprofen and naproxen sodium and the para-aminophenols, represented by acetaminophen.

The mechanism of action of the NSAIDs is based on the inhibition of the COX isoenzymes, COX-1 and COX-2.Non-selective NSAIDs inhibit both COX-1 and COX-2, whereas COX-2 specific inhibitors have a minimal effect on COX-1.COX-1 stimulates prostaglandin synthesis, regulates platelet aggregation and modulates vascular homeostasis, the mucosal integrity of the GI tract and the functioning of the renal system.COX-2 is a key mediator of inflammation and it is induced in response to inflammatory stimuli.

The analgesic effects of NSAIDs have been attributed to the inhibition of COX-2, while the GI side effects are thought to be derived from the inhibition of COX-1. NSAID's use has long been associated with GI side-effects, including dyspepsia, heartburn and nausea. The risk for developing GI complications is greater in patients who are treated with high doses of NSAIDs or treated for extended periods of time and also in patients who take multiple NSAIDs concomitantly.

Plants used for anti-inflammatory activity[16,22,23]

Plants are one of the most important sources of medicine. Herbal drugs have regained their popularity in treatment against various diseases. Plant medicines are great importance in the primary healthcare in many developing countries. According to World Health Organisation still about 80% of the world population rely mainly on plant-based drugs. Most of the medicinal plant parts are used as raw drugs and they possess varied medicinal properties. Medicinal plants play an important role in the development of potent therapeutic agents and can be used in preventive, promotional and curative applications. Herbal medicine generally uses various parts of plants or mixtures of plant extracts to treat illness, to promote health, to restore the body's ability to protect, regulate and heal by itself. Natural ingredients are more easily and more readily metabolized by the body so they produce fewer, if any, side effects and provide increased absorption in the bloodstream resulting in more thorough and effective treatments. Also many herbal remedies are reported to have serious side-effects, adverse effects and some of them have a tendency to interact with the synthetic preparations. The phytoconstituents responsible for anti-inflammatory activity include alkaloids, glycosides, terpenoids, resins, essential oils, polysaccharides, flavonoids, cannabinoids, steroids, fatty acids, phenolic compounds, etc.

Plants having anti-inflammatory activity

Sl. no.	Plant name	Family	Plant part
1	Aconitum heterophyllum	Valeraneaceae	Root
2	Adhatoda vasica	Acanthaceae	Leaves
3	Aloe vera	Asphodelaceae	Leaves
4	Azardirachta indica	Meliaceae	Leaves
5	Baccharis incarum	Astereae	Whole plant
6	Bacopa monnieri	Scrophulariaceae	Whole plant
7	Boswellia serrata	Burseraceae	Resin
8	Cassia fistula	Caesalpiniaceae	Leaves
9	Citrus auranticum	Rutaceae	Fruit
10	Commiphora mukul	Burseraceae	Resin
11	Curcuma longa	Zingiberaceae	Rhizomes
12	Emblica officinalis	Euphorbiaceae	Fruit
13	Lantana camera	Verbenaceae	Leaves
14	Lycopodium clavatum	Lycopodiaceae	Aerial parts
15	Magnifera indica	Anacardiaceae	Bark
16	Moringa olifera	Moringaceae	Root, flower
17	Piper longum	Piperaceae	Roots
18	Ricinus communis	Euphorbiaceae	Roots, leaves
19	Sida cordifolia	Malvaceae	Whole plant
20	Sidium guajava	Myrtaceae	Fruit
21	Tuberaria lignosa	Cistaceae	Leaves
22	Vinca rosea	Apocynaceae	Leaves
23	Visnea mocanera	Theaceae	Leaves
24	Vitex negundo	Lamiaceae	Leaves
25	Zingiber officinale	Zingiberaceae	Rhizome

Novel drug delivery system[12,13,21,26]

The novel carriers should ideally fulfil two prerequisites. It should deliver the drug at a rate directed by the needs of the body, over the period of treatment and it should channel the active entity of herbal drug to the site of action. The nano sized novel drug delivery systems of herbal drugs have a potential future for enhancing the activity and overcoming problems associated with plant medicines.

A variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsion, microsphere, etc. has been reported using bioactive and plant extracts. The various drug delivery systems include liposomes, microparticles, resealed erythrocytes, pharmacosomes, etc.

Liposomes are one amongst the various drug delivery system used to target the drug to particular tissue. Their size ranges from 25-500nm. The main advantages of using liposomes include high biocompatibility, easiness of preparation, chemical versatility, simple

modulation of their pharmacokinetic properties. Delivery of agents to the reticuloendothelial system (RES) is easily achieved using liposomes as drug carrier. Liposomes are superior carriers and have the ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. It also has affinity to keratin of horny layer of skin. Liposomal formulations are widely used in the pharmaceutical field as drug delivery systems due to their versatility and clinical efficacy and they have been used to administer drugs by several routes such as the oral, parenteral and topical. Among these, topical delivery of drugs carried by liposomes exhibit interesting applications. Topical liposome formulations could be more effective and less toxic than conventional formulations.

What is liposome?[3,8]

Liposomes are self-assembled (phospho) lipid -based drug vesicles that form a bilayer (uni-lamellar and/or a concentric series of multiple bilayers (multilamellar) enclosing a central aqueous compartment. The size of liposomes ranges from 30nm to the micrometer scale, with the phospholipid bilayer being 4-5 nm thick. Different administration routes, such as parenteral, pulmonary, oral, transdermal, ophthalmic and nasal routes have been developed to improve therapeutic efficacy and patient compliance.

As drug vehicles, liposomes exhibit outstanding properties, such as protecting the encapsulated substances from physiological degradation, extending the half-life of the drug, controlling the release of drug molecules and excellent biocompatibility and safety. Liposomes can selectively deliver their payload to the diseased site through passive and/or active targeting, thus decreasing the systemic side-effect, elevating the maximum-tolerated dose, and improving therapeutic benefits.

Designing of liposomes is done to achieve the following optimized properties:

1. Drug loading and control of drug release rate.
2. Overcoming the rapid clearance of liposomes.
3. Intracellular delivery of drugs.
4. Receptor-mediated endocytosis of ligand -targeted liposomes.
5. Triggered release.
6. Delivery of nucleic acids and DNA.

Mechanism of liposome formation[8]

Liposomes are formed by phospholipids (Amphiphilic molecules having a hydrophilic head and hydrophobic tail). The hydrophilic part is mainly phosphoric acid bound to a water soluble molecule whereas the hydrophobic part consists of two fatty acid chains with 10-24 carbon atoms and 0-6 double bonds in each chain. They form lamellar sheets when dispersed in aqueous medium by aligning themselves in such a way that the polar head group faces outwards the aqueous region while fatty acid groups face each other forming a spherical vesicle like structures called as liposomes. The polar fraction remains in contact with the aqueous region along with the shielding of the non-polar part. When phospholipids are hydrated in water, along with the input of energy like sonication, shaking, heating, homogenization, etc. It is the hydrophilic/hydrophobic interactions between lipid-lipd, lipid-water molecules that lead to the formation of bilayered vesicles inorder to achieve a thermodynamic equilibrium in the aqueous phase. Phospholipids are the main components of the cell membrane hence they possess excellent biocompatibility with amphiphilic properties. The amphiphilicity provide it the property of self-assembly, emulsifying and wetting characteristics. When phospholipids introduced into aqueous milieu, they self-assemble and it generates different structures with specific properties at different conditions.

Classification of liposomes[8]

1. **Based on structural features**

- Multilamellar large vesicles
- Oligolamellar vesicles
- Unilamellar vesicles
- Small unilamellar vesicles
- Medium sized unilamellar vesicles
- Large unilamellar vesicles
- Giant unilamellar vesicles
- Multivesicular vesicles

2. **Based on method of liposome preparation**

- Single or oligolamellar vesicle made by reverse phase evaporation method
- Multilamellar vesicles made by reverse phase evaporation method
- Stable plurilamellar vesicles
- Frozen and thawed MLV

- Vesicles prepared by extrusion method
- Vesicles prepared by fusion
- Vesicles prepared by French press
- Dehydration-rehydration vesicles
- Bubblesomes

3. Classification based on targeting concepts of liposomes

- PEGylated liposomes
- Immunoliposomes
- Cationic liposomes
- Thermosensitive liposomes

Mechanism of action of liposomes[8]

A liposome consists of a region of aqueous solution inside a hydrophobic membrane. Hydrophobic chemicals can be easily dissolved into the lipid membranes; in this way liposomes are able to carry both hydrophilic and hydrophobic molecules. Steps involved in liposome action of drug delivery include adsorption, endocytosis, fusion, lipid exchange.

Therapeutic applications of liposomes[8,17]

- Site-avoidance delivery
- Site specific targeting
- Intracellular drug delivery
- SR drug delivery
- Intraperitoneal administration
- Immunological adjuvants in vaccines

CONCLUSION

NSAIDs are not useful in all cases because of their side effects like GIT irritation, liver dysfunction, etc. Medicinal plants have been used as source of wide variety of biologically active compounds and used extensively as crude material or as pure compounds for treating various diseases. Due to the toxicity and side-effects of allopathic medicines, herbal medicines are becoming popular. Using NDDS we can deliver herbal drugs to the desired site and thereby overcome the difficulties associated with the conventional dosage forms containing herbal drugs. Liposomes are one of the novel drug delivery system used to entrap various drugs such as hydrophilic and lipophilic, irrespective of their solubility. By the use of

a suitable drug carrier medicaments can be effectively delivered to their target site. Liposomes can reduce toxicity and enhance the efficacy.

REFERENCE

1. Joseph C. Maroon, Jeffrey W. Bost, Adara Maroon. Natural anti-inflammatory agents for pain relief. *Surgical neurology international*, 2010; 1(80): 6-10.
2. Harsh Mohan. Textbook of Pathology. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd, 2010; 6: 130-135.
3. Peng Liu, Guiliang Chen, Jingchen Zhang. A Review of Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives. *Molecules*, 2022; 27(1372): 1-23.
4. Linlin Chen, Huidan Deng, Hengmin Cui, Jing Fang, Zhicai Zuo, Junliang Deng, Yinglu Li, Xun Wang and Ling Zhao. Inflammatory responses and inflammation-associated diseases in organ. *Oncotarget*, 2018; 9(6): 7204-7218.
5. Abolfazl Akbarzadeh, Rogaie Rezaei-Sadabady, Soodabeh Davaran, Sang Woo Joo, Nosratollah Zarghami, Younes Hanifehpour, Mohammad Samiei, Mohammad Kouhi and Kazem Nejati-Koshki. Liposome: Classification, Preparation and Applications. *Nanoscale Research Letters*, 2013; 8(102): 1-9.
6. B.V. Mitkari, S. A. Korde, K.R. Mahadik and C.R. Kokare. Formulation and Evaluation of Topical Liposomal Gel for Fluconazole. *Indian Journal of Pharmaceutical Education and Research*, 2010; 44(4): 324-333.
7. Darya A. Kuznetsova, Elmira A. Vasilieva, Denis M. Kuznetsov, Oksana A. Lenina, Sergey K. Filippov, Konstantin A. Petrov, Lucia. Ya. Zakharova, Oleg G. Sinyashin. Enhancement of the Transdermal Delivery of Nonsteroidal Anti-inflammatory Drugs using Liposomes containing Cationic Surfactants. *ACS Omega*, 2022; 7: 741-750.
8. Yadav D, Sandeep K, Pandey D, Dutta RK. Liposomes for Drug delivery. *Journal of Biotechnology and Biomaterials*, 2017; 7(4): 1-8.
9. Dr. Rakesh P. Patel, Hardik Patel, Ashok H. Baria. Formulation and Evaluation of Liposomes of Ketoconazole. *International Journal of Drug Delivery Technology*, 2009; 1(1): 16-23.
10. Asmita Singh, Prerana Vengurlekar, Sudha Rathod. Design, Development and Characterisation of Liposomal Neem Gel. *International Journal of Pharma Sciences and Research*, 2014; 5(4): 140-144.

11. M. Kamra, A. Diwan, S. Sardana, Topical Liposomal Gel: A Review. *International Journal of Pharmaceutical Sciences and Research*, 2017; 8(6): 2408-2414.
12. Kant Shashi, Kumar Satinder, Prashar Bharat. A Complete Review on: Liposomes. *International Research Journal of Pharmacy*, 2012; 3(7): 10-16.
13. Susanta Paul, Mayukh Jana, Anannya Bose, Sunirmal Bhattacharjee, Joyeeta Guha Roy, Puja Chakraborty. Topical Liposomal Gel: A New Strategy of Novel Drug Delivery. *World Journal of Pharmacy and Pharmaceutical Sciences*, 2017; 6(1): 568-577.
14. Yogesh S.Thorat, Nagesh S. Kote, Virendra V. Patil, Avinash H. Hosmani. Formulation and Evaluation of Liposomal Gel containing extract of Piprine. *International Journal of Current Pharmaceutical Research*, 2020; 12(3): 126-129.
15. Lisa Sercombe, Tejaswi Veerati, Fatemeh Moheimani, Sherrry Y. Wu, Anil K. Sood, Susan Hua. Advances and Challenges of Liposome Assisted Drug Delivery. *Frontiers in Pharmacology*, 2015; 6(286): 1-10.
16. Sarwar Beg, Suryakanta Swain, Hameed Hasan, M Abdul Barkat, Md Sarfaraz Hussain. Systematic review of herbals as potential anti-inflammatory agents: Recent advances, current clinical status and future perspectives. *Pharmacognosy Reviews*, 2011; 5(10): 120-137.
17. Utpalendu Jana, Rabindra Nath Chattopadhyay, Badri Prasad Shaw. Preliminary Studies on Anti-inflammatory Activity of Zingiber officinale Rosc., Vitex negundo Linn. and Tinospora cordifolia (Willid) Miers in Albino rats. *Indian Journal of Pharmacology*, 1999; 31: 232-233.
18. Sandeep Kalepu, Sunilkumar K T,Sudheer Betha ,Mohanvarma M. Liposomal drug delivery system -A Comprehensive Review. *International Journal of Drug Development and Research*, 2013; 5(4): 62-75.
19. A Mark Fendrick, Bruce P Greenberg. A review of the benefits and risks of nonsteroidal anti-inflammatory drugs in the management of mild-to-moderate osteoarthritis. *Osteopathic Medicine and Primary Care*, 2009; 3(1): 1-7.
20. V. Kusum Devi, Nimisha Jain, Kusum S. Valli. Importance of novel drug delivery systems in herbal medicines. *Pharmacognosy Reviews*, 2010; 4(7): 27-31.
21. Ajazuddin, S.Saraf. Applications of novel drug delivery system for herbal formulations. *Fitoterapia*, 2010; 81: 680-689.
22. S. Kumar, BS. Bajwa, Singh Kuldeep, AN. Kalia. Anti-Inflammatory Activity of Herbal Plants: A Review. *International Journal of Advances in Pharmacy, Biology and Chemistry*, 2013; 2(2): 272-281.

23. Sunita Verma. Medicinal plants with anti-inflammatory activity. *The Journal of Phytopharmacology*, 2016; 5(4): 157-159.
24. Abdullatif Azab, Ahmad Nassar, Abed N Azab. Anti-Inflammatory Activity of Natural Products. *Molecules*, 2016; 21(1321): 1-19.
25. Mona Ghasemian, Sina Owlia, Mohammed Bagher Owlia. Review of Anti-Inflammatory Herbal Medicines. *Advances in Pharmacological Sciences*, 2016; 10(1155): 1-11.
26. M. Karma, A. Diwan, S. Sardana. Topical Liposomal Gel: A Review. *International Journal of Pharmaceutical Sciences and Research*, 2017; 8(6): 2408-2414.