REVIEW OF LITERATURE

Medicinal and aromatic plants have played vital role in alleviating human sufferings as therapeutic agents since times. Work has been done in this field for identification of active principles of medicinal plants and investigation of the extracts in order to ensure that they are safe, effective and of constant activity. Plant materials are used in various forms having excellent biological activity for the welfare of human being.

Nowadays numerous polymers are being used in pharmaceutical formulations containing active plant constituents for treatment of diseases which are not yet curable with literal mechanism. Hydrogels containing specific polymers have attracted the concentration of researches towards their use in dermatological formulations.

Various plants containing flavonoid as principle constituent are used for antioxidant, wound healing and antimicrobial activity and their drug delivery mechanism is now widely used for development of such formulations.

In this area of research, Javed et al., 2013 prepared seed extracts of two different plants viz. Phoenix dactylifera and A. squamosa, by methanol extraction method at the ratio of 1:2 using 100ml volume of methanol and stock concentration of 50mg/ml in dimethyl sulfoxide (DMSO) of each extract was made. The extracts and fractions were tested for antimicrobial activity against standard microbial strains of Klebsiella pneumoniae (gram- negative), Staphylococcus aureus (gram-positive), Escherichia.coli (gram-negative), Salmonella typhi (gram-negative), Enterococcus faecalis (grampositive), Pseudomon aerugenosa (gram-negative) and Salmonella paratyphi (gram-negative) by means of Agar-Disc diffusion method and minimal inhibitory concentration (MIC) was noted . The test culture of standard microbial cultures was 3 X 105 CFU/ml and standard antibiotic used was Ampicillin with clavulanic acid. In this context, two extract from traditional plants, Custard Apple (A. squamosa) and Dates (Phoenix dactylifera) were used alone or in combination to
assess their antimicrobial efficacy against both Gram negative and Gram positive bacterial clinical isolates.

*A. squamosa* (Annonaceae) has also been proven to have anthelmintic activity by *Satyanarayana et al.* in 2013. They investigated the anthelmintic activity in leaf extract using adult earthworm, *Peritima posthuma*. The hexane, ethylacetate, ethanolic extracts of the crude drug at concentrations of 100mg/ml, 200mg/ml, were tested which involve determination of paralysis time and death time. Albendazole (10mg/ml) was used as standard and it was found that the *A. squamosa* leaf extracts showed dose dependent activity in ethyl acetate extract at a dose of 200mg/ml with significant action.

Traditionally, *A. squamosa* (AS) has been used as ethnomedicine and various parts of the plant have been used to combat several disorders including dysentery, cancer and hyperthyroidism. Since the twig of this plant is reported to contain a large number of alkaloids, *Soni et al.*, 2013 chose to study its medicinal properties on the immune response of BALB/c mice. They evaluated the immunomodulatory activity in the crude ethanolic extract and its four fractions, viz. hexane (F1), chloroform (F2), n-butanol (F3) and aqueous (F4) prepared from the twigs of AS to locate the active constituents in the fractions. The extract and fractions were fed orally at 3, 10 and 30 mg/kg for 14 consecutive days and mice were euthanized to assess various immune parameters. The ethanolic extract and its three fractions F2, F3 and F4 were found active since they increased splenic T and B cellular proliferation with a significant accentuation in peritoneal macrophage function, differentially increased the CD4+, CD8+ T lymphocytes and CD19+ B lymphocytes. The extract and its active fractions also demonstrated significant Th1 or Th2 mixed cytokine response at almost all doses tried in a dose-dependent manner.

Fruit peel of *A. squamosa* has also been undertaken to investigate the effect of various extracts on blood glucose and lipid profile in streptozotocin induced diabetic rats by *Sharma et al.*, 2013. Different extracts (Petroleum ether, Ethyl acetate and Alcoholic) of *A. squamosa* fruit peel was administered orally (250mg/kg body weight) for 21 days. Effects were estimated in streptozotocin induced diabetic rats.
The effects were compared with glibenclamide. The treatment with alcoholic extracts of *A. squamosa* fruit peel and Glibenclamide resulted in a significant reduction of blood glucose. The alcoholic extract also resulted in a significant decrease in lipid profile. The decreased blood glucose and lipid profile clearly showed the antidiabetic and antihyperlipidemic effect of *A. squamosa* fruit peel extract.

Low back pain is an extremely common illness syndrome that causes patient suffering and disability and requires urgent solutions to improve the quality of life of these patients. Treatment options aimed to regenerate the intervertebral disc (IVD) are still under development. The cellular complexity of IVD, and consequently its fine regulatory system, makes it a challenge to the scientific community. Biomaterial based therapies are the most interesting solutions to date, whereby tissue engineering and regenerative medicine (TE&RM) strategies are included. By using such strategies, i.e., combining biomaterials, cells, and biomolecules, the ultimate goal of reaching a complete integration between native and neo-tissue can be achieved. Hydrogels are promising materials for restoring IVD, mainly nucleus pulposus (NP). Use of hydrogels in a cellular and cellular strategies for intervertebral disc regeneration has been studied by *Pereira et al* in 2013. To better understand IVD and its functioning, they focused on several aspects: anatomy, pathophysiology, cellular and biomolecular performance, intrinsic healing processes and current therapies. In addition, the application of hydrogels as NP substitutes was addressed due to their similarities to NP mechanical properties and extracellular matrix.

Many drugs and drug candidates are suboptimal because of short duration of action. For example, peptides and proteins often have serum half-lives of only minutes to hours. One solution to this problem involves conjugation to circulating carriers, such as PEG, that retard kidney filtration and hence increase plasma half-life of the attached drug. *Gary et al.*, 2013 recently reported an approach to half-life extension that uses sets of self-cleaving linkers to attach drugs to macromolecular carriers. The linkers undergo β-eliminative cleavage to release the native drug with predictable half-lives ranging from a few hours too very; however, half-life extension becomes limited by the renal elimination rate of the circulating carrier. An approach
to over coming this constrain is to use non-circulating, biodegradable S.C. implants as drug carriers that are stable throughout the duration of drug release.

An approach for application of cell penetration to selective small interference RNA (siRNA) localized delivery system, cell penetrable nano-polyplex assembled hydrogel system was presented by Young-Min Kim et al. in 2013. The cell penetrable nano-polyplex assembled hydrogels prepared by protamine conjugation to poly (organophos-phazene) and inducement of nano-polyplexes with siRNAs. After an injection of cell penetrable nano-polyplex solution into the body, it turns into a gel due to thermosensitivity of poly(organophosphazene). The gel maintains up to 4 weeks and the released 30 nm-sized nano-polyplexes from the gel induces highly effective siRNA delivery due to cell penetration. The new system showed a high gene silencing efficiency on only the target site in long-term with a single injection.

Regenerative efficacy of an injectable hyaluronic acid/mildly crosslinked alginatehydrogel (HA/ALG hydrogel) containing human adipose-derived mesenchymal stem cells (hAdMSCs) for vocal fold (VF) wound healing have been investigated recently by Kim et al., 2013. Endoscopic evaluations were performed at 1 and 3 months after injury, and functional evaluations of mucosal vibration and viscoelastic properties were carried out post-euthanization at 3 months after injury. Histopathologic and immunohistochemical evaluations of extracellular matrix (ECM) components and of hepatocyte growth factor (HGF) activity were conducted in injured VFs. The engraftment of implanted hAdMSCs was investigated by detecting fluorescent-labeled cells. The administration of hAdMSCs and hAdMSCs in HA/ALG hydrogel produced better macroscopic morphologies than the injection of PBS. Histologic evaluations revealed that treatment with hAdMSCs in HA/ALG produced more favorable ECM changes than hAdMSC.

The bioactive and compressive properties of photopolymerisable polyethylene glycol hydrogels was improved with the incorporation of hydroxyapatite at different loadings by Killion et al. in 2013. The synthesis of pure hydroxyapatite was verified through Fourier transform infrared spectroscopy (FTIR) analysis by the complete reaction of all constituents. The formation of a bioactive layer of the hydrogel based
composites was confirmed through the formation of carbonate hydroxyapatite after soaking the samples in simulated body fluid.

Carboxy methyl chitosan (CM-chitosan) and gelatin hydrogels by radiation cross linking were also prepared by Huang et al. in 2013. A pre-clinical study was performed by implantation model and full-thickness cutaneous wound model in Sprague-Dawley rats to preliminarily evaluate the biocompatibility, biodegradability and effects on healing. In the implantation test, as a component of the hydrogels, CM-chitosan showed a positive effect on promoting cell proliferation and neovascularization, while gelatin was efficient to stabilize the structure and prolong the degradation time. In addition to this, Singh et al., 2013 studied and explored the potential of these materials in designing new hydrogel wound dressings meant for slow release of gentamicin, an antibiotic drug, and to enhance the wound healing potential. The hydrogel films were characterized by SEM, FTIR, XRD and swelling studies. Biomedical properties of hydrogel films like blood compatibility, antioxidant activity, mucoadhesion, antimicrobial activity, oxygen/water vapor permeability, microbial penetration and mechanical properties (tensile strength, burst strength, resilience, relaxation, and folding endurance) have been evaluated. The histological studies of wound healing were also carried out on swiss albino mice of strain Balb C and it has been observed that in case of wounds covered with hydrogel dressings shown faster wound healing, formation of well developed fibroblasts and blood capillaries as compared to open wounds.

The influence of Aloe vera on water absorption and the in-vitro degradation rate of Aloe vera-Ca-alginate hydrogel films for wound healing and drug delivery applications were investigated in 2013 by Pereira et al. The influence of A. vera content (5%, 15% and 25%, v/v) on water absorption was evaluated by the incubation of the films into a 0.1M HCl solution (pH 1.0), acetate buffer (pH 5.5) and simulated body fluid solution (pH 7.4) during 24h. Results showed that the water absorption has significantly higher for films containing high A. vera contents (15% and 25%), while no significant differences were observed between the alginate neat film and the film with 5% of A. vera. Effect of FLAMIGEL (hydrogel dressing) on the repair of residual burn wound was also evaluated by Yang et al., 2013. Sixty burn patients
with residual wounds hospitalized in 6 burn units from November 2011 to May 2012 were enrolled in the multi-center, randomized, and self-control clinical trial. Two residual wounds of each patient were divided into groups T (treated with FLAMIGEL) and C (treated with iodophor gauze) according to the random number table. On post treatment day (PTD) 7 and 14, wound healing rate was calculated, with the number of completely healed wound counted. Furthermore, Jaiswal et al., 2013 developed the bi-layer dressing of gelatin nanofibrous mat loaded with epigallocatechin gallate (EGCG)/poly vinyl alcohol (PVA) hydrogel and evaluated on full-thickness excision wounds in experimental Wistar rats. Nanomorphological observation, porosity, effect of crosslinking on tensile strength, physical stability and drug release profile in phosphate buffer and biocompatibility aspects of electrospun nanomat were investigated by various physico-chemical tools. EGCGa release profile was found to increase from 2-4 days with decreasing crosslinking time from 15 to 5 min.

Biodegradable in situ gel-forming controlled drug delivery system composed of curcumin loaded micelles and thermosensitive hydrogel was developed by Gong et al., 2013 and applied for cutaneous wound repair. Curcumin is believed to be a potent antioxidant and anti-inflammatory agent. Due to its high hydrophobicity, curcumin was encapsulated in polymeric micelles (Cur-M) with high drug loading and encapsulation efficiency. Cur-M loaded thermosensitive hydrogel (Cur-M-H) was prepared and applied as wound dressing to enhance the cutaneous wound healing. Cur-M-H was a free-flowing sol at ambient temperature and instantly converted into a non-flowing gel at body temperature. For better efficacy, Pulat et al. 2013 prepared a novel wound dressing material which provides burst release of an antibiotic in combination with sustained release of growth factor delivery. This might be beneficial for the prevention of infections and to stimulate wound healing. As a wound dressing material, the semi-interpenetrating network (semi-IPN) hydrogel based on polyacrylamide (PAAm) and chitosan (CS) was synthesized via free radical polymerization. Ethylene glycol dimethacrylate was used for cross-linking of PAAm to form semi-IPN hydrogel. The hydrogel shows high water content (~1800%, in dry basis) and stable swelling characteristics in the pH range of the wound media (~4.0-7.4).
Thick hydrogel films composed of alginate and Aloe vera gel in different proportions (95:5, 85:15 and 75:25, v/v) was prepared and evaluated by Pereira et al., 2013 regarding the light transmission behavior, contact angle measurements, and chemical, thermal and mechanical properties. These thin hydrogel films, prepared by cross-linking reaction using 5% calcium chloride solution, were also investigated relatively to their water solubility and swelling behavior. Results showed that Aloe vera improved the transparency of the films, as well their thermal stability. The developed films present adequate mechanical properties for skin applications, while the solubility studies demonstrated the insolubility of the films after 24h of immersion in distilled water. The water absorption and swelling behavior of these films were greatly improved by the increase in Aloe vera proportion.

Than et al. 2013 developed new keratin-based hydrogel wound dressing and applied to the neck of a patient who was suffering from recessive dystrophic epidermolysis bullosa. A significant improvement was observed in the robustness of skin in this area: reduced propensity to blister and improved healing of blisters. The improvement allowed the cessation of use of secondary dressings for this area. The factors gave a significant improvement in quality of life for the patient.

The effect of Brassica oleracea herbal balsam on the healing of skin wounds in rats was investigated by Rebolla et al., 2013. Twenty four rats (Wistar, 60 days, 250 g) were divided into four groups: untreated animals (C) and treated with the ointment (T), subdivided into two experimental times (seven and 16 days). A 3cm² skin wound was made in the back of all animals. 100 ml of the Brassica oleracea was applied twice a day in T group. Biometric analysis was made with images captured at one, four, seven, ten, 13, and 16 days. At seven and 16 days, animals of each group were euthanized. The wound area removed was processed for histological and histomorphometric analysis to quantify birefringent collagen fibers. Statistical analysis was made considering p < 0.05 as significant. Similarly, Chusri et al., 2013 studied wound healing-related biologic activities of traditional herbal formulas used for wound treatment in southern Thailand. Water and ethanol extracts of the formulas (THR-SK004, THR-SK010, and THR-SK011) were tested for their antibacterial potency against methicillin-resistant Staphylococcus aureus (MRSA) and -susceptible
S. aureus. Anti-inflammatory activities of the extracts were assessed by detection of the inhibition of lipopolysaccharide-induced nitric oxide production.

Antimicrobial properties of plants are used traditionally to treat TB and related symptoms against microorganisms (Klebsiella pneumoniae, Staphylococcus aureus, and Mycobacterium aurum A+) associated with respiratory infections using the microdilution assay. Madikizela et al., 2013 selected ten plants were selected based on a survey of available literature of medicinal plants used in South Africa for the treatment of TB and related symptoms. The petroleum ether, dichloromethane, 80% ethanol, and water extracts of the selected plants were evaluated for antibacterial activity. Out of 68 extracts tested from different parts of the 10 plant species, 17 showed good antimicrobial activities against at least one or more of the microbial strains tested, with minimum inhibitory concentration ranging from 0.195 to 12.5 mg/mL. In the search of wound healing activity of plants and their active constituents, Sivasankaridevi et al., 2013 also studied antimicrobial activity of acetone extract of four plants against two standard bacterial pathogens, viz. Escherichia coli and Staphylococcus aureus by agar cup method and disc method. The leaves of the following plants were used in this study viz. Moringa (Moringa oleifera), Betel (Piper betle), Jack (Artocarpus heterophyllus) and Basumathi leaf (Pandanus sp).

Of the four leaves tested, the leaf extracts of betel exhibited activity against the gram negative bacteria, Escherichia coli. Betel showed inhibition zone (15.0 mm) in disc method which is on par (17.0 mm) with that of Streptomycin (1000 ppm). Further, Nenaah in 2013 studied antimicrobial activity of solvent extracts and flavonoids of Calotropis procera growing wild in Saudi Arabia and evaluated using the agar well-diffusion method. A bioassay-guided fractionation of the crude flavonoid fraction (Cf3) of MeOH extract having highest antimicrobial activity led to the isolation of four flavonoid glycosides as the bioactive constituents. Structure of compounds have been elucidated using physical and spectroscopic methods including (UV, IR, (1)H, (13)C-NMR, DEPT, 2D (1)H-(1)H COSY, HSQC, HMBC and NOESY). Compounds were found to be the 3-O-rutinosides of quercetin, kaempferol and isorhamnetin, besides the flavonoid 5-hydroxy-3,7-dimethoxyflavone-4'-O-β-glucopyranoside. The phytochemical composition, antimicrobial and radical-scavenging activities of
Acalypha manniana (Euphorbiaceae) methanol leaf extract and its fractions were also evaluated by Noumedem et al., 2013. The methanol extract was partitioned into hexane, ethyl acetate and residual fractions and phytochemical analysis was conducted using standard methods. The broth microdilution method was used to evaluate the antimicrobial activity against nine bacterial species and four dermatophyte species. The free radical scavenging activities of the methanol extract and its fractions were evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay.

Elobieta et al., 2013 studied antibacterial activity of quercetin, morin, sodium salt of quercetin-5i-sulfonic acid (NaQSA) and sodium salt of morin-5i-sulfonic acid (NaMSA) were tested against six bacterial strains: Escherichia coli (ATCC 25922 and clinical isolates - ESBL ), Pseudomonas aeruginosa (ATCC 27853 and clinical isolates - carbapenem resistant), Staphylococcus aureus (ATCC 29213 and clinical isolats- MRSA). The most effective inhibitors against the model strain S. aureus are NaQSA and NaMSA (MIC = 3.9 µg/mL). Among polyhydroxylavones used in this investigation, morin exhibits the highest antibacterial activity against tested strains. Antioxidant, antibacterial and cytotoxicity activities of the flavonoid compound (F1) extracted from Capsicum annum L. Seeds were also studied by Adnan et al., 2013. The compound showed greater antibacterial activity against gram positive (Staphylococcus aureus, and Streptococcus aureus) bacteria than gram negative (Klebsiella pneumonia, Pseudomonas aeruginosa and E. coli) using the disc diffusion method. The extract showed high activity against Streptococcus aureus with a zone of inhibition (40 mm) than that of E. coli (20 mm) at a concentration of 60 mg/ml. Antioxidant, reducing power and chelating of ferrous ion activities were also significantly higher in the flavonoid compound (F1).

Herbal hydrogel incorporated with the extract of Ipomea pes-tigridis was formulated and evaluated for anti acne activity by Sandhya et al., 2013. The FTIR studies showed that there were no drug excipient interactions. The anti acne and anti inflammatory activity showed an activity comparable to that of the standard drugs clindamycin and diclofenac, respectively. Hence it can be concluded that the formulation can be a good substitute for the existing synthetic anti acne agents. Adedapo et al., 2013 also studied anti-inflammatory and analgesic activity of
Lagenaria breviflora fruit. The anti-inflammatory activity of the aqueous leaf extract of the plant was assessed using carrageenan-induced paw edema and histamine-induced paw edema in rats. The analgesic effect was determined using the acetic acid writhing method as well as formalin test in mice. Our results showed that the extract at 100 and 200mg/kg body weight significantly reduced the formation of the oedema induced by carrageenan and histamine. In the acetic acid-induced writhing model, the extract showed a good analgesic effect characterized by reduction in the number of writhes when compared to the control.

**Bouratoua et al., 2013** screened the antioxidant and antibacterial activities of two flavonoides: isorhamnetin-3-O-rutinoside and isorhamnetin-3-O-rubinobioside isolated from n-butanol and ethyl acetate extracts of Calotropis procera (Asclepiadaceae), which were characterized by the use of combined spectral methods (UV-visible, NMR) in addition of acid hydrolysis. The antioxidant activity and the total phenolic content, as well as the influence of petroleum ether, chloroform and methanol extracts from the leaves of Gynotroches axillaris, on micro-organisms was also studied by **Salam et al., 2013**. The total phenolic contents were evaluated by using Folin-Ciocalteu reagent and the obtained values ranged from 70.0 to 620 mg GAE/g. The efficiency of antioxidation, which was identified through the scavenging of free radical DPPH, exhibited that the highest IC_{50} was in the methanolic extract (44.7 µg/mL) as compared to the standard ascorbic acid (25.83 µg/mL) and to standard BHT (17.2 µg/mL). In vitro antimicrobial activity of extracts was tested against Gram-negative bacteria, Gram-positive bacteria and fungi. Furthermore, **Semwal et al., 2013** also evaluated antioxidant potential and effectiveness of Equisetum arvense in treatment of wounds and burns. The methanolic extract was obtained by soxhlet extraction and then the herbal gel was prepared using the extract in different proportion and different ingredients. The gel was evaluated using the parameters like appearance, pH, spreadability, drug release, rheological proerties, extrudability. Free radical scavenging activity of herbal gel prepared from Equisetum arvense was measured using DPPH method, Nitric oxide method and H_{2}O_{2} assay method. Antioxidant potential of Cleome gynandra L. and Maerua angolensis DC (Forsk) was evaluated by **Meda et al., 2013** also. The n-hexane (n-H),
dichloromethanic (DCM), acetonitrile (ACN), ethyl acetate (EA), methanolic (MeOH) and n-butanol (n-BuOH) fractions of each species. They quantified the total phenolic and total flavonoid contents in different fractions. The whole of the tests were evaluated with a sample concentration at 100µg/mL and three methods i.e., FRAP, ABTS and DPPH were used to estimate the total antioxidant capacity of the plant fractions. The total phenolic and total flavonoid contents were also determined spectrophotometrically using Folin-Ciocalteu and AlCl₃ reagents, respectively. Butanolic fractions gave the best anti-FRAP (535.961 µmol AAEAC/g of fraction), anti-ABTS (155.868 µmol TEAC/g of fraction) and anti-DPPH (81.109 µmol QEAC/g of fraction) activities. In this series of work, Zhen et al., 2013 also studied antioxidant activity of Ganoderma lucidum. The results showed that herbs could significantly affect the scavenging capacity of Ganoderma extracts on different free radicals. Based on the composition analysis of bioactive components in Ganoderma, the contents such as polysaccharides and triperpenoids in Ganoderma were changed due to the addition of herbs; moreover, they could be assimilated into Ganoderma. The bioactive component change in Ganoderma due to the addition of herbs revealed an important impact to its scavenging capacity on different free radicals. Therefore, the compositions of cultivation medium were highly correlated with bioactive components and pharmacological action of Ganoderma.

Dua et al., 2013 investigated antimicrobial properties of methanolic extract of Fennel (Foeniculum vulgare Miller). The extract, rich in flavonoids (9.325 ± 1.25 mg QE/g dry seeds) was subjected to HPLC analysis for identification and quantification of phenolic contents. Gallic acid (277.131µg), caffeic acid (166.062µg), ellagic acid (99.476µg), quercetin (781. 986µg) and kaempferol (92.856µg)/g dry seeds were identified. Antibacterial activities of methanolic extract of dried fennel seeds were determined against pathogenic bacteria Bacillus pumilus, Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli by determining cell damage, growth inhibition zone and minimum inhibitory concentration.

Earlier these kinds of studies had also been done by number of researchers in the field of hydrogels as well as plants and their active constituents to get remarked wound healing activity. Varadharajan et al., 2012 did the phytochemical analysis
of ethanolic extract of *A. squamosa* leaf. The analysis revealed the presence of carbohydrates, alkaloids, flavonoids, tannins, terpenoids, quinones and glycosides in the ethanolic leaf extract. Further characterization of the bioactive principles in the ethanolic crude extract was done by TLC, HPLC and HPTLC. TLC profiling of ethanolic leaf extracts reveals the presence of numerous phytochemicals. Different Rf (Retention factor) value of various phytochemicals provide valuable information regarding their polarity and selection of solvents for separation of phytochemicals. HPLC revealed the presence of Rutin, Quercetin, Kaempferol, Farmarixetin, and Isorhamnetin in the ethanolic leaf extract. The efficacy of ethanolic extract of *A. squamosa* leaves was also examined by Thangave *et al.*, 2012 on wound repair in streptozotocin–nicotinamide-induced diabetic rats by excision wounds model on rats. The drug at a dosage of 100 mg/kg body wt was reconstituted in 200 µl of phosphate buffered saline and applied topically once daily for the treated wounds. The control wounds were left untreated. Wound tissues formed on days 4, 8, 12 and 16 (post-wound) were used to estimate DNA, total protein, total collagen, hexosamine and uronic acid.

Patil *et al.*, 2012 studied comparative anti-inflammatory activity of hydrogels containing herbal hydro-alcoholic extracts of *Pterocarpus marsupium*, *Pterocarpus santalinus* and *Glycyrrhiza glabra*. Hydroalcoholic solvent ethanol: water in 70:30 proportions was used for the extraction by continuous hot extraction using soxhlet apparatus. The herbal hydrogels containing 10% extract as API were formulated using chitosan as gel base, by chemical crosslinking of chitosan with glutaraldehyde. Anti-inflammatory activity of herbal hydrogels was evaluated by carrageenan induced rat hind paw edema method.

Wound healing activity of hydrogel containing a mixture of poloxamers 407 and 188 used for the matrix of the MISG was determined by Du *et al.*, 2012. Other ingredients include aminocaproic acid (to stop bleeding), povidone iodine (anti-infective), lidocaine (pain relief), and chitosan (to enhance wound healing and regeneration). The incipient gelation temperature of the MISG was modified by varying the poloxamer concentration. Poloxamer cytotoxicity was evaluated in addition to the effect of the MISG on hemostasis in rabbits, pain relief in mice,
bacteriostasis in vitro, and wound healing. The optimal MISG matrix consisted of 30% (w/v) poloxamer (407/188, 1:1, w/w) solution and was able to change to a gel within 10 minutes at 37°C. In 2012, Chakavala et al. also developed new hydrogel containing silver sulfadiazine (SSD) for enhanced burns wound healing. The hydrogel was prepared by cross-linking of PVA and Chitosan by freeze thawing method. Their gel properties, moisture retaining capacity, fluid uptake capacity, in vitro release study, in vivo burn healing effect were evaluated. Chitosan and PVA cross linking decreased gel fraction upto 70% determined the good gel properties. This cross linked hydrogel increased the Swelling ratio and Water vapor transmission rate (WVTR) which provides the sustained release of drug and moist environment for healing respectively. The hydrogel containing 7.5% of PVA, 0.75% of chitosan found to have increased gel strength, higher water vapor transmission rate and fluid uptake capacity suitable for faster healing of burns. This hydrogel also sustained the release of 1% SSD required for longer antimicrobial activity and found better in vivo burn healing capacity as compared to marketed preparation. Hydrogel containing normal collagen at low concentration (0.66 mg/ml) was also formulated by Helary et al., 2012. The effect of raised collagen concentration on hydrogel stability, cell growth, apoptosis and fibroblast phenotype was evaluated over 21 days in culture. In contrast to NCHs, CCH5s were more stable because no contraction was observed during the first week. CCH5 favored cell proliferation and protected fibroblasts against apoptosis. At day 21, cell number assessed in CCH5 was around one million, i.e about 10 times higher than in NCH. Matrix metalloproteinases detection appeared lower in CCH5 than in NCH. In CCH5, fibroblasts exhibited a sustained collagen I gene expression for 14 days, while it was inhibited from day 4 in NCH. Moreover, gene expression of KGF was constant in CCH5 and that of VEGFA increased from day 7. Modi et al., 2012 prepared polyherbal hydrogel by using different combination of extract of Symplocos racemosa and Acorus calamus and oil of Coriandrum sativum and evaluation was done by biologically and physically, like pH, viscosity, spreadability, and Texture analyzer. Antimicrobial activity was performed against S. epidermis and E. coli. Optimized formula is 0.5% carbopol, 5% ethanol (95%), triethanolamine 0.5%, extract ratio 2:2:1 (of Symplocos racemosa and Acorus calamus and oil of
Coriandrum sativum) and sufficient quantity of water. This formulation showed 24 mm and 20 mm ZI against S. epidermis and E. coli. respectively by using agar cup plate method. pH of hydrogel was 6.90 and its viscosity and spreadability was 14840cps and 4.620g.cm/sec respectively. Formulation possesses more antimicrobial activity. Formulation was kept at 40°C±2°C/75% RH ±5% RH for one month, no significant change was observed after 7th, 14th and 30th days (by evaluating parameters like pH, viscosity and antimicrobial activity). Polyherbal hydrogel was stable upto one month and it has shown potent antimicrobial activity as compared with the marketed formulation.

Thangavelu et al., 2012 evaluated antibacterial, antioxidant and wound healing properties of seven traditional medicinal plants from India in experimental animals. The ethanolic and aqueous extracts of Azadirachta indica, Emblica officinalis, Terminalia bellirica, Terminalia chebula, Curcuma longa, Cleome gynandra, Triticum aestivum, Vitis vinifera L – Black Raisins (Zante Currants) and brown raisins (Sultanas) were investigated for in vitro antioxidant, antibacterial and wound healing activity. The free radical scavenging activity was studied in vitro by measuring DPPH, reducing power, hydrogen peroxide scavenging and total antioxidant assays of these plant extracts. Antibacterial activities were evaluated against five microorganisms using agar well diffusion method. The wounds were created on the skin of the rabbits by crushing the Paederus fuscipes beetles and applying the pederin which produced inflammation and wound after two days. In this series of research to identify and evaluate plant materials as wound healing agents, Balekar et al., 2012 investigated the wound healing potential of Wedelia trilobata (L.) leaves. An ethanolic extract of Wedelia trilobata leaves was subjected to column chromatography. Hexane, ethyl acetate (WEA) and chloroform:methanol (50:50) (WCM) fractions were obtained. The fractions were tested using relevant in vitro wound healing assays. Antioxidant activity was measured by the DPPH assay. The fibroblast proliferation, oxidative stress using hydrogen peroxide, an in vitro scratch assay and increasing collagen content was determined using fibroblast L929. Minimum inhibitory concentrations (MICs) were determined against Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, and Pseudomonas aeruginosa.
Prasannabalaji et al., 2012 also investigated in vitro antibacterial activity of various solvent extracts of Indian traditional medicinal plants i.e Ocimum sanctum, Ocimum gratissimum, Aegle marmelos, and Adhatoda vasica leaves against clinical pathogens of human origin. The antimicrobial activity of different solvents crude extract of four medicinal plants used in traditional Indian medicine was tested by disc diffusion method against five bacterial pathogens: Escherichia coli, Staphylococcus aureus, Salmonella typhi, Salmonella paratyphi and klebsiella pneumoniae.. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) was determined for evaluating the potential plant extract.

Different parts of the plant A. squamosa had been investigated to show different pharmacological actions. Chandrashekar and Kulkarni, 2011 isolated and determined the chemical constituents of leaves of A. squamosa from ethanolic extract. The chemical compound isolated was analyzed by IR, LC, MS and the compound was confirmed flavones type compound on the basis of spectral data. In vitro anti-microbial activity of isolated (AS-1) compound from leaf extract of A. squamosa was studied by the agar diffusion method. Two gram positive (Staphylococcus aureus; Bacillus subtilis), two negative (Pseudomonas aeruginosa; Salmonella typhi) bacterial stains and two fungal stains (Aspergillus flavus, Aspergillus niger), selected for screening. The screening results showed that highest zone of inhibition was observed with isolated compound against Pseudomonas aeruginosa (MIC:100 µg/ml) Staphylococcus aureus; Bacillus subtilis. (MIC:200 µg/ml) and Salmonella typhi. (MIC: 400µg/ml). But in their study, antifungal activity was not shown by the isolated (AS-1) compound. Hayath and Subramanian in 2011 also worked on the same plant. They designed & evaluated the anti-diabetic and antioxidant potential of A. squamosa Linn. (Annonaceae) in STZ-induced experimental diabetes in rats. Daily oral administration of A. squamosa leaves extract (100 mg/kg b.w./day) to diabetic rats for 30 days significantly reduced the levels of blood glucose, glycosylated hemoglobin, urea and creatinine. The observed decrease in the levels of plasma protein, plasma insulin, C-peptide and hemoglobin in the diabetic rats were elevated to near normal by the extract treatment. The altered antioxidant status of diabetic rats were reverted back to near normally by the
administration of *A. squamosa* leaves extract. The efficacy of the *A. squamosa* extract was comparable with gliclazide, a known hypoglycemic drug. **Gomez et al., 2011** also studied the antimicrobial and anti-inflammatory potential of the Swedish bitter herbal extract was evaluated, using pure microbial cultures and clinical samples of 29 patients. It was observed that the extract caused significant (p<0.05) in vitro growth inhibition of up to 29%, 17%, 15%, and 50% against *Prevotella intermedia*, *Bacteroides forsythus*, *Porphyromonas gingivalis* and *Streptococcus intermedius* respectively. In addition, the extract significantly (p<0.05) inhibited oral flora growth in patient samples showing MICs of < 7.8 µg/ml in 21% of the patients, 15.6 µg/ml in 17% of the patients, 31.2 µg/ml in 10% of the patients, 62.5 µg/ml in 17% of the patients, 125 µg/ml in 3% of the patients, and 250 µg/ml in 7% of the patients and induced a maximum of 75% growth inhibition as measured by the MTT reduction assay.

A mechanism for hydrogel formation was proposed and the structure of the product was established using Fourier transform infrared spectroscopic(FT-IR) and scanning electron microscopy (SEM) by **Sadeghi and Soleimani** in 2011. They prepared intelligent starch-based superabsorbent polymers (SAP) to be used as pH carriers for the controlled delivery of metronidazole loaded drug. The swelling behavior of these polymers was investigated in various salt solutions. Finally, the effects of pH, and levels of loaded drug on drug release profile in various surrounding media were investigated. Release profiles of metronidazole, a water-soluble drug, from the hydrogels were studied under both simulated gastric and intestinal pH conditions. **Kumar and Verma** in 2011 studied the chemical stability of optimized bioadhesive topical gel. For that bioadhesive topical gel formulation was optimized on the basis of bioadhesive strength and in-vitro drug permeation study of prepared bioadhesive topical gel. To attain the motto of present study, BNTGs were prepared using natural bioadhesive polymer Aegel marmelos (plant Bale) and hydroxyethyl cellulose (HEC). Bioadhesive strength of BNTG3 was found to be 1.72±0.023 gm/cm2. BNTG3 permeates only 89.00%±0.59% over 24 h. The self life of BNG3 was found to be 0.439 years and 0.302 years at 25±2°C and 40±2°C, respectively. Half-life of BNTG3 was found to be 2.902 years and 1.996
years at 25±2°C and 40±2°C, respectively. Activation energy was found to be 4631.7003 cal/mol. All the data was found to be extremely significant by studying one way ANOVA at p<0.05 level. In last it was concluded that, BNTG3 will be more effective and stable if it is stored at or below 25±2°C. So, BNTG3 was successfully developed and standardized for improved topical therapeutics. Ulea et al, in 2011 prepared collagen-based biomaterials containing Thuja occidentalis tincture – 0.5, 1.0 and 1.5 mL tincture/100 g 1.1%. Collagen hydrogel were prepared as hydrogels having the pH 3.8 and 7.4 and porous matrices by hydrogels’ lyophilization. FT-IR and UV-CD spectra of hydrogels showed that thuja tincture does not disturb the triple helical conformation of collagen in the acid hydrogels, while rheograms, storage and loss modules suggest weak interactions with components from tincture. FT-IR spectra indicate a slight denaturation of collagen at pH 7.4 and a slight cross-linking, but the measurements were made for the hydrogels resulted by syneresis. FT-IR spectra confirmed the preservation of triple helical conformation of collagen and a slight cross-linking in all the matrices. SEM shows an agglomeration of fibrils and an increase of pore size and irregularity which increase with thuja tincture amount that can be assigned to cross-linking.

Wound healing potential of hydrogel obtained from pigeon pea (Cajanus cajan) seed husk was evaluated in albino rats by Patil and Mastiholimath in 2011. Pigeon pea seed husk polysaccharide was successfully extracted and utilized in the preparation of gel formulation. Gel formulation showed significant antibacterial activity against both gram positive and gram negative selected bacteria. Rat excision wound model was used to screen the wound healing activity. Percentage closure of original wound area was calculated on various days and results indicated that the percentage wound closer and epithelialization for the gel formulation treated group was comparable with those of standard group treated with Band aid. A gel formulation of aceclofenac using four types of gelling agents: carbopol, hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose sodium (Na-CMC) and sodium alginate was prepared by Patel et al., 2011 in order to decrease the gastric ulcerogenic effects. Effect of penetration enhancer (propylene glycol) on the release has been studied. The gels were evaluated for physical appearance,
rheological behavior, drug release and stability. The drug release from all gelling agents through a standard cellophane membrane was evaluated using Keshary-Chien diffusion cell. All gels showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value. Among all the gel formulations, carbopol showed superior drug release than followed by Na-CMC, HPMC and sodium alginate. Drug release decreased with increase in polymer concentration and it was not linearly proportional with the concentration of penetration enhancer or co-solvents. Stability studies showed that the physical appearance, rheological properties, and drug release remained unchanged upon storage for two months at ambient conditions.

Gel containing methanolic leaf extract of Aspila africana was analyzed for its potency on experimentally-induced wound in rats by Attama et al., 2011. Wounds were inflicted on Wistar rats using excision model. The extract was formulated as hydrogel and xerogel. The wound healing effects of the formulations were compared to that of a standard antibiotic, Cicatrin® together with the gel bases. In all cases, there was a progressive decrease in wound area with time. A 100% wound closure was observed by the 17th day post wound in both gel formulations of the extract and the standard. It was concluded that the extract formulated in gel forms were effective in healing wounds. Dash et al., 2011 also evaluated the wound healing activity of the petroleum ether, chloroform, methanol and aqueous extracts of the leaves of Argemone mexicana Linn. (Family: Papaveraceae) in rats using excision (normal and infected), incision and dead space wound models respectively. The effects of test samples on the rate of wound healing were assessed by the rate of wound closure, period of epithelialization, wound breaking strength, weights of the granulation tissue, determination of hydroxyproline, super oxide dismutase (SOD), catalase and histopathology of the granulation tissues. Nitrofurazone (0.2% w/w) in simple ointment I. P. was used as reference standard for the activity comparison. The results of the study revealed that the animals treated with methanol and aqueous extracts of A. mexicana showed faster rate of wound healing compared to other extracts under study. The present work justified the use of the leaves of A. mexicana for wound healing activity as claimed in the folklore literature.
**Shrivastava and Gupta** in 2011 evaluated the anticancer properties of aqueous and methanolic extracts of chamomile against various human cancer cell lines. Exposure of chamomile extracts caused minimal growth inhibitory responses in normal cells, whereas a significant decrease in cell viability was observed in various human cancer cell lines. Chamomile exposure resulted in differential apoptosis in cancer cells but not in normal cells at similar doses. HPLC analysis of chamomile extract confirmed apigenin 7-O-glucoside as the major constituent of chamomile; some minor glycoside components were also observed. Apigenin glucosides inhibited cancer cell growth but to a lesser extent than the parent aglycone, apigenin. In 2011, **Naira & Karvekar** isolated Gallic acid (GA), rutin(R), quercitin (Q), ellagic acid (EA) and sitosterol (S) from the methanolic extract of the leaves of *Tectona grandis*. They formulated as 0.2 % ointment in emulsifying base and evaluated for their wound healing activity. The formulation containing rutin was subjected to stability testing. There was no change in color, pH and no phase separation.

The anti-inflammatory activity of polyherbal formulation of leaves of *A. squamosa* and rhizome of *Curcuma longa* was assessed by **Sharma et al., 2010**. The polyherbal formulation showed the significant anti-inflammatory activity comparable to the standard drug Indomethacin against carrageenan induced rat paw edema method. The polyherbal formulation reduced the inflammation induced by carrageenan by 49.3% and 61.73% on oral administration at 100 mg/ kg and 200 mg/kg, respectively as compared to the control treated group an analgesic activity comparable to the standard drug tramadol HCl. **Vanitha et al., 2010** also used the same plant in their study. They investigated antioxidant effect of leaves of *A. squamosa* and *Aegle marmelos* by using different *in-vitro* models like DPPH, ABTS, nitric oxide, super oxides and lipid peroxidation. The result revealed that *A. squamosa* (500 μg/mL) showed maximum activity using DPPH where as Aegle marmelos showed maximum scavenging activity using ABTS. Both of them reduced the production of free radicals in a dose dependent manner. The result showed that the alcoholic leaf extract of *A. squamosa* and *Aegle marmelos* may possess different compounds (Tannins, flavonoids etc.) which have potent antioxidant activity exhibited differently.
Acetogenins from *Annona genus* plant seeds was extracted by Haijun *et al.*, 2010 using supercritical carbon dioxide under optimized conditions and a high-performance liquid chromatography (HPLC) method was established for simultaneously determining ten AcGs. All of the ten compounds were simultaneously separated on reversed-phase C18 column (250 mm × 4.6 mm, 5 μm) with the column temperature at 30°C. The mobile phase was composed of (A) methanol and (b) distilled water, the flow rate was 1.0 ml/min and the detection wavelength was set at 220 nm. The established method showed good precision and accuracy with overall intra-day and inter-day variations of 0.99-2.56% and 1.93-3.65%, respectively, and overall recoveries of 95.16-105.01% for the ten compounds analyzed. The established method can be applied to evaluate the intrinsic quality of Annonaceae plant seeds.

Antioxidant and antiradical activities of *Cassia tora* were investigated by Lobo *et al.*, 2010. They evaluated and compared the antioxidant activity, total phenolics, flavonoids content of aqueous (AETB) and ethanolic (EETB) extracts of fruits. The antioxidant activity was assessed by DPPH (1,1–diphenyl–1,2–picrylhydrazyl), ABTS (2,2-Azino-bis3-ethylbenothiazoline-6-sulfonicacid diammonium salt), nitric oxide, superoxide and hydroxyl radical scavenging assay, FRAP (Ferric Reducing Antioxidant Power), reducing power and TAC (Total antioxidant capacity). Two different aqueous (AECT) and ethanolic (EECT) extracts were used in this studied.

A topical gel formulation of etoricoxib, which would attenuate the gastrointestinal related toxicities associated with oral administration, was developed by Ravi *et al*. in 2010. In their study, gels with carbopol, HPMC K4M, MC, HPC were prepared with different permeation enhancers like, MSO, lemongrass oil, menthe oil, oleic acid. They were evaluated for physicochemical properties, drug release. After in-vitro evaluation of gel formulations, ex-vivo permeation of etoricoxib was evaluated across rat epidermis and human cadaver skin. The best formulation was then evaluated for the anti-inflammatory and skin irritation study. Goheland *et al.*, 2010 also formulated hydrogel thickened ibuprofen transdermal formulation. Eutectic mixture of camphor and menthol was chosen as oily phase solvent for ibuprofen and powerful penetration enhancer Tween 80, ethanol (90% v/v) and
carbopol 940 were selected as surfactant, co-surfactant and hydrogel thickening agent respectively. Ternary phase diagrams were constructed to obtain the concentration range of eutectic mixture surfactant and co-surfactant for microemulsion formulation. Hydrogel thickened microemulsions were characterized for pH, viscosity, spreadability, irritation study and in vitro drug transport study with excised rat skins. The average drug transport rate of optimized hydrogel thickened microemulsion containing 1% w/w ibuprofen, 31.84% w/w eutectic mixture of camphor and menthol, 27.21% w/w tween 80, 13.61% w/w ethanol, 23.84% w/w water, 1.5% w/w carbopol 940 and 1% w/w triethanolamine through rat skin was 1.94 µg/ml.h.cm.

Elaeagnus angustifolia (EA) topical gel (19%) efficacy was determined by Jamileh et al., 2010 in the treatment of symptomatic oral lichen planus. Twenty-eight patients (m/f: 7/21) with symptomatic oral lichen planus participated in the study. Fifteen patients (m/f: 4/11) received EA gel and 13 patients (m/f: 3/10) received placebo. There was a 75% decrease in pain (33.3% in the case and 7.7% in the control groups) and a decrease of 50% in size (33.3% in the case group). Whereas, Nicolynn et al., 2010 prepared modular protein polymer based hydrogels through genetic engineering and enzymatic crosslinking. Animal derived tissue transglutaminase (tTG) and recombinant human transglutaminase (hTG) enzymes were used for coupling two classes of protein polymers containing either lysine or glutamine, which have their cognition substrates for enzymatic cross linking evenly spaced along the protein back bone. Furthermore, the modular hydrogel composition allows tailoring of mechanical and physical properties for specific tissue engineering applications.

Constanţa Sava and Rodica Sirbu in 2010 developed spectrophotometric method for determination of flavonoid from marine algae. The precision, accuracy, specificity, and the quantification limit of the method were verified. The calibration curve traced for the concentrations domain 2-32mg/L rutin - AlCl₃ was used to determine the flavonoid content expressed in rutin of Black Sea algae. Whereas in the same duration, Shah et al., 2010 developed sensitive, simple, and accurate high-performance liquid chromatographic method for determination of rutin and quercetin both simultaneously in Azadirachta indica leaf powder. The chromatographic
separation was performed on Phenomenex C18 column (250 x 4.6, 5 µm) with a 60:40 v/v mixture of methanol and 0.1% O-phosphoric acid in water at the flow rate of 1.2 mL/min and detection at 258 nm, with a run time of 10.0 min. The developed method was then validated using statistical analysis. Prior to these works, Santagati et al., 2008 had already developed high-performance liquid chromatography method using a diodearray detector(DAD) for the simultaneous analysis of five major catechins: (+)-catechin (C), (−)-epicatechin (EC), (−)-gallocatechin (GCT), (−)-epigallocatechin (EGC), (−) (EGCG), and the phenolic plant metabolites gallic acid (GA) and rutin (RT) in lyophilized extract of Cistus species.

Researches had been concentrating on the mechanism on wound healing since long time. Paula et al., 2006 reported the effects of several natural compounds on the proliferation of human bone marrow and human CD34 and CD133 cells. A dose-related effect of blueberry, green tea, catechin, carnosine, and vitamin D3 was observed on proliferation with human bone marrow as compared with human granulocyte-macrophage colony-stimulating factor (hGM-CSF). We further show that combinations of nutrients produce a synergistic effect to promote proliferation of human hematopoietic progenitors. This demonstrates that nutrients can act to promote healing via an inter-action with stem cell populations.

In 1992, number of researchers formulated and evaluated different kinds of hydrogels varying in the polymer contents. Dolz-M., et al., 1992 investigated the rheological behavior of a low concentration carbomer 940 (carbopol 940) hydrogel with varying concentration of triethanolamine (trolamine; a neutralizer) 5 formulations with triethanolamine concentrations between 0.052% and 0.10% to create pH ranges between 5.78 and 6.83 and evaluated for shear rate, viscosity and thixotropic behavior. These characteristics were then compared to thixotropic area determined by Ostwald's model. Results indicated that gel stability was greatest at pH 6.29. The value predicted by Ostwald's model and those obtained from the experiment were comparable. Bucktan & Tawburic 1992 investigated the effect of varying concentrations of propylene glycol on the drug release from carbopol (carbomer) hydrogels at four- different temperature using chlorhexidine as a model drug and the value of compensation analysis for studies of drug release from gel formulation was
discussed. Thermodynamic functions were calculated from the temperature dependence of apparent diffusion constants, using a modified Arrehenius approach. A common mechanism of release was suggested for gels containing propylene glycol but a different mechanism occurred in the carbopol hydrogels without the added glycol.

Lu et al., 1992 studied the effect of various chemical enhancers and vehicles for their ability to improve the in-vivo percutaneous absorption of leuprolide acetate in nude mouse, snake and cadaver skin in either Franz diffusion cells or a Bronaugh flow through system using HPLC assay. Maximum permeability, enhancement of leuprolide acetate was achieved with a non irritating formulation containing ethyl alcohol, menthol, camphor, methyl salicylate, urea and Klucel EF (HPMC). The effects of chemical enhancers on skin permeability were highly dependent on the skin model used. Turunen & Utti 1992 reviewed the role of penetration enhancers in transdermal drug delivery including general rules governing percutaneous absorption, classification of enhancers and their functional properties and system design considerations. Seth in 1992 studied a comparative pharmacokinetics and bioavailability study of percutaneous absorption of diclofenac from two topical formulations containing drug as a solution gel or as an emulsion gel.

However other researchers also worked on the hydrogels and drug release profile prior to the studies discussed earlier. During 1991, various articles were reported having the similar studies. Chi & Jun 1991 studied the release pattern of 0.2%-0.3% ketoprofen from topical gel formulations containing 20%-30% poloxamer 407 using a membraneless diffusion cell to determine the effects of polymer content, drug and ethyl alcohol concentration, pH and temperature on drug release. Drug release exponentially as the polymer concentration increases over the 24 – 45°C temperatures with the Arrhenius function. The change of the pH from 3 to 6 substantially increased drug release rate. An observed enhanced drug release in the presence of ethyl alcohol was attributed to the decrease in gel viscosity with higher drug loading in the gel. An increase in the release rate but a reduction of drug diffusion coefficient was observed. Drug release profile has also been studied by other researchers. In 1991, Babar & Bhandari studied the in-vitro release pattern of chlorpheniramine maleate from gel bases containing 2% hydroxypropylmethylcellulose (methocel KM 100) modified
hydrophilic bases and white petrolatum using cellulose membrane and hairless mouse skin as diffusion barrier. Effect of urea, ethyl alcohol and dimethyl sulfoxide to enhance drug release from the formulations was also studied. Takayama & Nagi 1991 optimized the ketoprofen gel formulation using (+) limonene and ethyl alcohol on absorption enhancers. Takayama K, Kikuchi K, Chata Y. (1991) studied the percutaneous absorption of indomethacin from gel ointment formulation in rats. Optimization of formulation was done by ethanol and terpene (+) limonene. The synergism of ethyl alcohol and (+) limonene was examined and found to be significant.

Niazy 1991 evaluated the influence of oleic acid and other permentation promoters dodecanoic acid (lauric acid), urea, on in-vitro release pattern of dihydroergotamine using improved Franz diffusion cells with dorsal rabbit skin as the barrier membrane, Oleic acid was the most effective enhancer tested, increasing the percutaneous absorption of dihydroergotamine by 208-fold. Bommannan D., Okuyama H., 1991 used high frequency ultrasound to enhance transdermal drug delivery of salicylic acid from gel formulations. Brain., et al., 1991 studies the effect of laurocapram (Azone) on the percutaneous absorption of methotrexate, from alcoholic gel formulations an abdominal human skin mounted in all glass Franz type diffusion cells.

Some other research work related to these studies has been briefly discussed here. Origani M., et al.,1990 studied a two phase study to assess the efficacy and tolerability of topical oxatamide iT, one patient with pruritus vulves from cream and gel formulations. Mohamed A.A & Ismails S 1990. investigated the effect of increasing viscosity using different polymer viscolizers as well as different gel formulations on the anaesthetic activity of lidocaine on rabbit eyes. Wiechers J.W., et al.,1990 studied the percutaneous absorption of triarninolone acetonide cream with Azone as penetration enhancer. Ogiso T & Shintani M 1990 studied the effects of a series of fatty acids on percutaneous absorption of proprnolol through rabbit skin using a gel base. Dodecanoic acid (lauric-acid) and Myristic acid at a fatty acid proprnolol molar ratio of 1: 1 were the most potent agents in increases skin penetration giving the largest penetration rate and penetration coefficient. Pfister W.
It, Hsien D S, 1990 designed the systems for transdermal delivery system that incorporate permeation enhancers, including possible interaction with drug, skin etc. Poelman, et al., 1989 proposed a new non-invasive technique for assessing the efficacy of topical non-steroidal anti-inflammatory drugs. Mura P., et al., 1989 studies the solubility and partition coefficient data of clonazepam in propylene glycol and polyethylene glycol of different molecular weight. In aqueous solution containing carbopol and co-solvent effect on release from the various hydrogels were studied using two diffusion cell assemblies. Rheograms of each gel system showed pseudoplastic flow curves with negligible hysterises, zero order release was observed. Both assemblies were equivalent in drug release profile and total drug release. Gianaccini B., et al., 1989 reviewed the formulation and therapeutic applications of traditional and non-traditional ophthalmic ointment bases. Hydrogels formulated from synthetic, semi-synthetic or natural polymers lattices and emulsions are discussed. Seki T., et al., 1989 studies the percutaneous formulations of zidovudine (Azidothymidine AZT:I) topical solution of on rat abdominal skin absorption of several 10% oleic acid water. Wango, et al., 1989 investigated the effect of various unsaturated cyclic urea on transdermal penetration enhancement activity and mouse toxicity from topical formulation of indomethacin.
Review of Literature