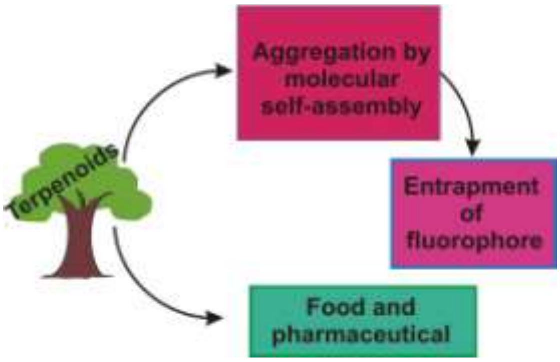
# MINI REVIEW ON MOLECULAR SELF ASSEMBLY AND APPLICATIONS OF NATURAL NANOSIZED TERPENOIDS

**Abstract**

Creation of supramolecular architectures by molecular self-assembly of small molecules has gained more attention by the research community due to diversified application of morphologies formed by such assemblies. Both the natural and synthetic molecules containing polar functional groups with hydrocarbon back bone are capable to form molecular self-assemblies. The advantages of the natural molecules over the synthetic molecules; they are less toxic, bio-compatible and biodegradable. Terpenoids, a group of plant secondary metabolites have tremendous significance due to renewable in nature, nanodimension, exhibit anti-bacterial, anti-viral, anti-oxidant, analgesic activity along with other biological activities. These molecules spontaneously self-assembled in various solvents to yield several types of morphologies like vesicles, fibers, tubes, petals and flowers etc. of macro to nanometric range. Some of the terpenoids are enable to produce supramolecular gel in single solvent or solvent mixtures. The self-assemblies are able to entrapment fluorophores and can be used to deliver drugs or remove toxic dye and pollutants




Graphical representation of source, self-assembly and applications of terpenoids.

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In this chapter I have discussed molecular self- assembly of some terpenoids, utilization of their self-assemblies along with the applications of terpenoids in food and pharmaceuticals.

**Keywords:** Terpenoids, Nano size, molecular self-assembly, application

## I. INTRODUCTION

Molecular self-assembly is a powerful phenomenon, which is borrowed from nature to fabricate novel supramolecular architectures. This process is proceeding without any guidance from outside. By definition it can be says that molecular self-assembly is a process of spontaneous organization of disordered small molecules in a medium under near thermodynamic equilibrium yielding stable supramolecular nano to micro-sized arrangements by virtue of non-covalent interactions. Several weak non covalent bonds like hydrogen bonding, electrostatic attraction, pi-pi interactions, van der-Waals interactions are mainly responsible for such process. Although these non-covalent interactions are relatively weak, the results of collective interactions through several such interactions lead stable self-assemblies. The supramolecular soft materials produced by self-assembly are highly responsive to different external stimuli e.g., temperature, pH, ultrasound, light etc[1,2]. The morphologies like vesicles, fibers, rods, tubes etc. fabricated by self-assembly of low molecular weight compounds are utilize in diversified fields like sensors, tissue engineering, drug delivery, nano technology etc[3,4,5].

Molecules containing various functional groups such as hydroxyl, carboxylic acid, amides, esters, sugars, steroids, nucleic acids, long chain alkanes can provide non-covalent interactions are enable to exhibit self-assembly process. In depth investigation on supramolecular self-assembly, it has been found that few natural product compounds having distinctive three-dimensional backbone with multiple functional groups have been extensively utilized as supramolecular self-assembly systems, such as steroidal skeletons, amino acids, and sugar skeletons etc[6].

Secondary plant metabolites are not as important as primary plant metabolites for the life of plant, but they play a significant role on plant itself like induce flowering, coloring of plants, attracting pollinators, protection from environmental stress, defense against harmful pathogens etc. and also exerts wide range effects on other living organisms. Terpenes, are the largest class of secondary plant metabolites containing several isoprene units. The origin of terpenes from isoprenes first hypothetically formulated by Otto Wallach but it is ignored until its general significance recognized by Ruzica who proposed the famous isoprene rule for biosynthesis of terpenes which states that all possible structures of terpenes can be derived mechanistically from certain olefins through enzymatic cyclization with rearrangements[7]. Terpenoids are another type of terpenes containing oxygen molecules that are constructed via biochemical modifications Terpenoids are classified into several categories depending upon isoprene units present in the molecule like hemi (C5), mono (C10), sesqui (C15), di (C20), sester (C25), tri (C30), sesquer (C35) and tetraterpenes (C40) consisting of one, two, three, four, five, six, seven and eight isoprene units respectively. Recently the plant metabolites have gained significant importance as source of organic molecules rather than petroleum based chemicals for their renewable and green nature to develop a sustainable society[8]. It has been revealed through computations that terpenoids from mono to tetra, all are nano sized[9,10]. These terpenoids also termed as renewable nano entities due to their inherent renewable nature. Most of the terpenoids contain asymmetric carbon atoms and have strong lipophilic tendency, soluble in organic solvents. Low molecular weight terpenoids like monoterpenoids are liquid where as di to tetra terpenoids are generally solid crystals. Terpenoids has crucial importance for treatment of various diseases; these can act as anticancer agents, antimicrobial, antiinflammatory, antioxidants, antiallergic, neuroprotective, antiaggregator, anti-coagulation, sedative and analgesic as well as source of several vitamins like A, E, K. These compounds are widely used in pharmaceutical, nutraceutical, food and beverage products, cosmetics, perfumes, synthetic chemicals, aroma and flavor additives, rubber products, and the bio-fuel industry[11]. Hence in one word it can be says that terpenoids are most essential compounds in everyday human life and health.

Terpenoids containing large hydrocarbon backbone with several polar functional groups are able to show molecular self-assembly property in several liquids. Some of these molecules are able to form strong gel in several organic liquids or binary liquid mixtures.

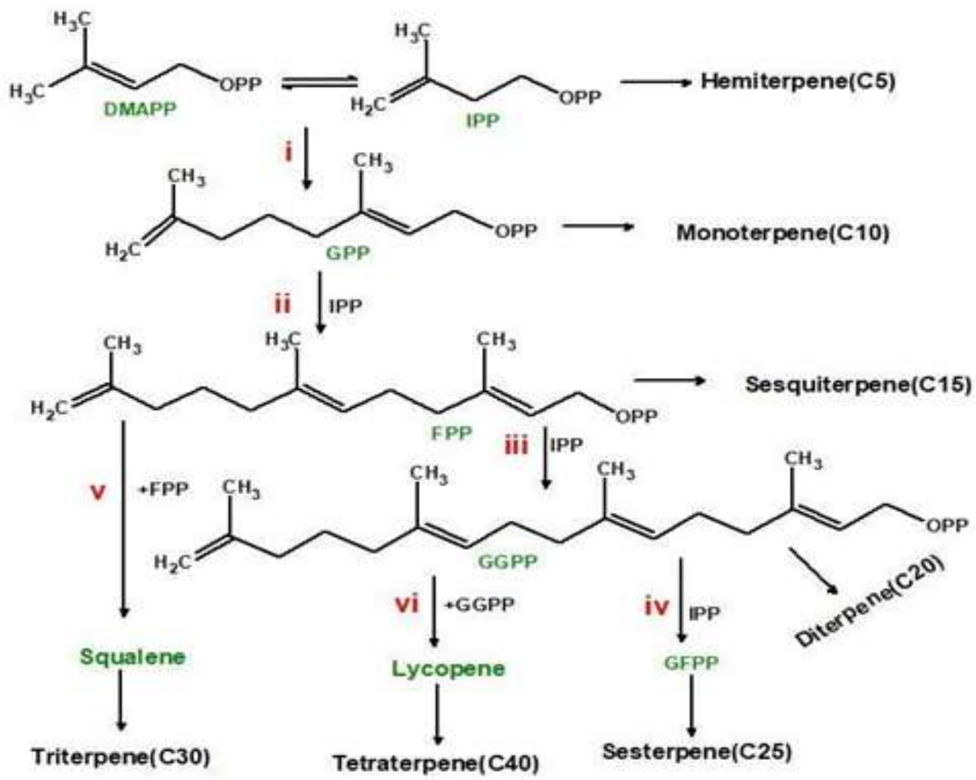


**Figure 1:** Schematic representation of bio-synthesis of terpenes fromisoprene precursor.

But the study of self-assembly property of terpenoids in literature is very few. In this chpater, I have tried to discuss the self-assembly studies of some nanosized diterperpenoids and triterpenoids along with utilization of self-assemblies towards entrapment of fluorophores. The applications of terpenoids in food and pharmaceutical products also been discussed.

## II. SELF-ASSEMBLY STUDIES OFTERPENOIDS

1. **Natural Terpenoids:** Though several types of terpenoids have been extracted from plants and studied their biological properties and used in food and pharmaceutical products, but study of self-assembly property is carried out only for few diterpenoid and triterpenoid molecules (Figure2).

Terpenoids having lipophilic hydrocarbon skeleton along with polar end groups like carboxylic acid or hydroxyl groups are generally insoluble or very poor soluble in water but show better solubility in polar organic solvents like DMSO, DMF or THF.

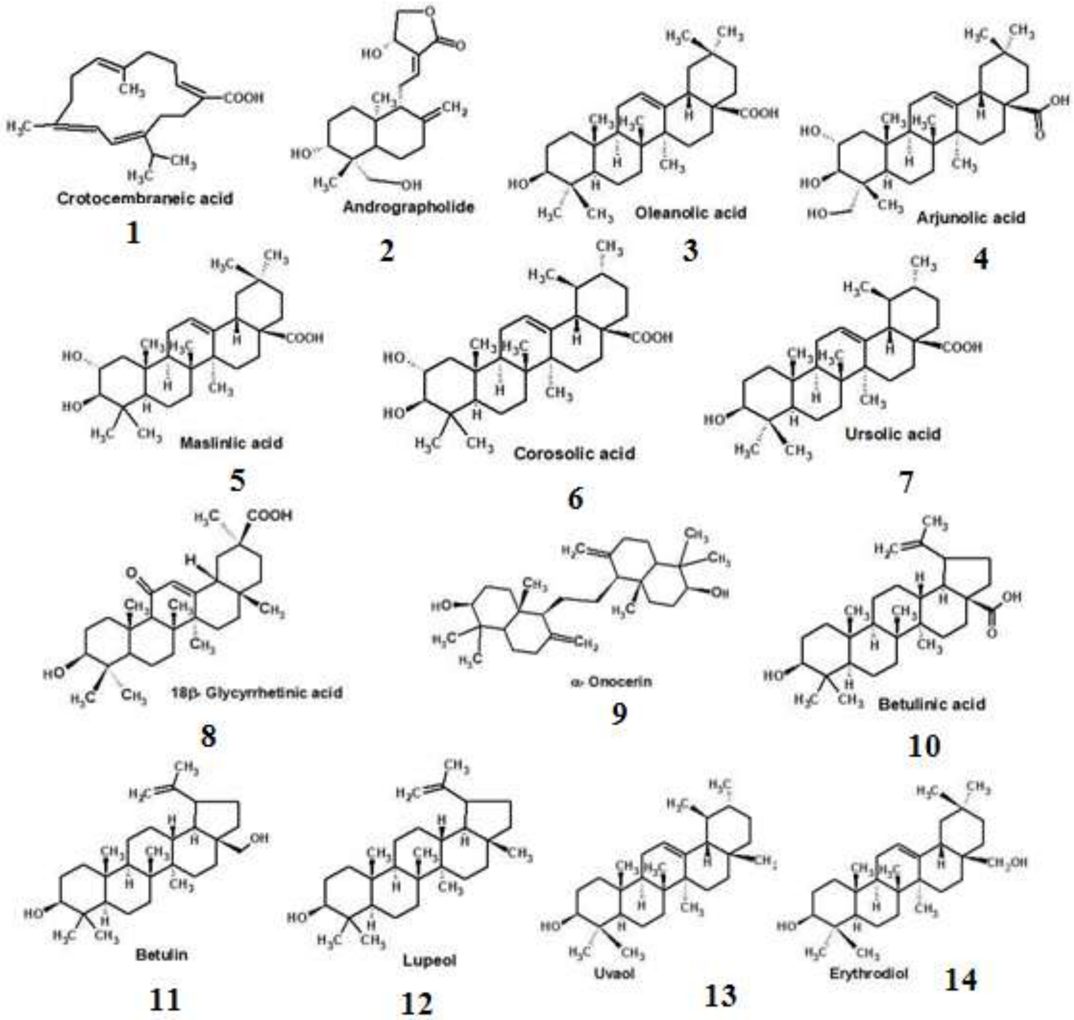


**Figure 2:** Different types of terpenoid molecules

The precursor geranylgeranyl pyrophosphate undergoes enzymatic cyclization with rearrangement to produce the diterpenoids which are C20 subset of terpenoids. A macrocyclic compound containing one carboxylic acid group crotocembraneic acid (**1**) with molecular size 1.12 nm is an example of diterpenoid and extracted from leaves of Croton oblongifolius Roxb [12]. This molecule spontaneously self-assembled in several aqueous organic binary solvent mixtures. Different microscopic studies revealed that this molecule produced nano to micro sized vesicular morphologies (Fig. 3a). Another example Andographolide(**2**), labdane type diterpenoid molecule consisting three polar hydroxyl groups with molecular length 1.28 nm extracted from the leaves of Androgra phispaniculata. This compound also yields vesicular morphologies (Fig. 3b) by molecular self-assembly in DMSO-water, DMF-water, THF-water and cyclohexanol water system [13].

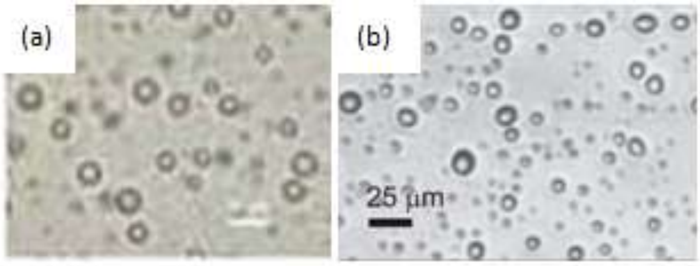


**Figure 3:** Optical microscopy images of self-assembled crotocembroneic acid (a), andrographolide (b).[12,13]

Triterpenoid molecules are bio-synthesized from the precursor oxido squalene. In literature example of triterpenoid molecules studied self-assembly property is more than that of diterpenoid molecules. The self-assembly property of an oleane type pentacyclic triterpenoid oleanolic acid (**3**), containing a hydroxyl and carboxylic acid group with molecular length1.45 nm extracted from the plant Lantana camara is first reported by Bag et al. This molecule exhibit self assembly property in different pure organic solvents like aromatic solvents, alcohols and chlorinated solvents etc. and also able to form strong gel.

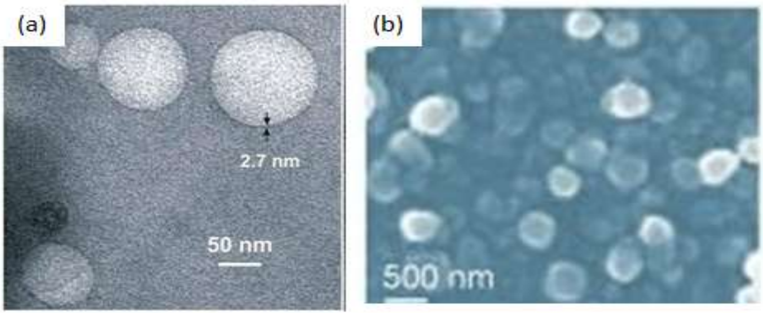


**Figure 4:** HRTEM images of dried self-assesmblies of arjunolic acid (a),Oleanolic acid (b).

Characterization of self-assemblies by several microscopic studies revealed that the vesicular morphologies (Fig.4b) are produced and vesicles are bilayer confirmed by XRD study.[14] Similarly, a tri hydroxyl pentaccylic triterpenoid arjunolic acid (**4**) extracted from saw dust of Terminalia arjuna spontaneously self-assembled in pure organic liquids as well asin aqueous binary solvents to form bilayer vesicular assemblies and also yields supramolecular gel. The wall thickness of the vesicles is 2.75 nm (Fig.4a) which is the twice of molecular size[15].

Oleane type dihydroxy triterpenoid maslinic acid (**5**) extracted from Olea Europaea with molecular size 1.67 nm self-assembled in different polar organic-aqueous solvent systems such as DMSO-water, DMF-water, ethanol-water[16]. Different microscopic studies revealed that morphologies by self-assembly of **5** are vesicular nature (Fig. 5a). Similarly the ursane type dihdroxy triterpenoid having molecular length 1.48 nm corosolic acid (**6**) obtained from leaves of Psidium guajava spontaneously undergoes self-assembly process in several binary solvent mixtures yielding vesicular morphology (Fig. 5b). This molecule isalso a supramolecular gelator and forms a strong gel in DMF-water (2:1, v/v) and ethanol- water (2:1, v/v) system[17]. Ursane type monohydroxy triterpenoid ursolic acid (**7**) obtained from the leaves of Plumeria rubra produces strong gel in several solvents, leading micro to nano sized vesicular along with tubular morphologies (Fig. 5c and 5d) by virtue of molecular self-assembly[18].

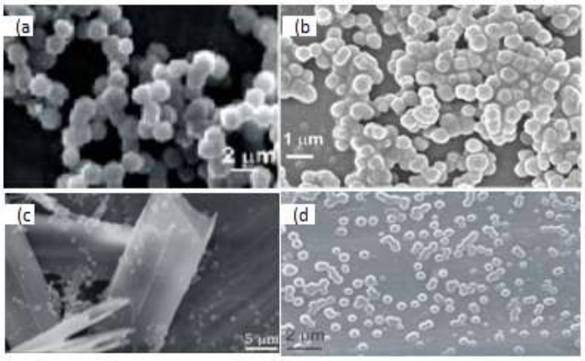


**Figure 5:** FESEM images of self-assembled maslinic acid (a),corosolic acid (b), ursolic acid (c,d)

Another example of triterpenoids are mono hydroxyl pentacyclic compound 18β-glycyrrhetinic acid (**8**) and dihydroxy C2 symmetric compound α-onocerin (**9**) isolated from Glycyrrhiza glabra[19] and Lycopodium clavatum[20] with molecular size 1.41 nm and 1.51 nm respectively exhibit self-assembly property in different organic solvents. These molecules yield flower like supramolecular architectures of nano to micro level (Fig.6a,6b). Monohydroxy triterpenoid betulinic acid (**10**) extracted from the bark of Ziziphus jujube spontaneously in self-assembled in 22 pure organic solvents and among them it produces strong gel in 19 solvents[21]. Characterization of self-assemblies revealed that this molecule with molecular size 1.31 nm yields fibrillar morphologies (Fig. 6c). But the triterpenoid betulin (1.29 nm) (**11**), obtained from the bark extract of Betula papyrifera (white Birch) produces flower like morphologies through self-assembly property. (Fig. 6d)[22].

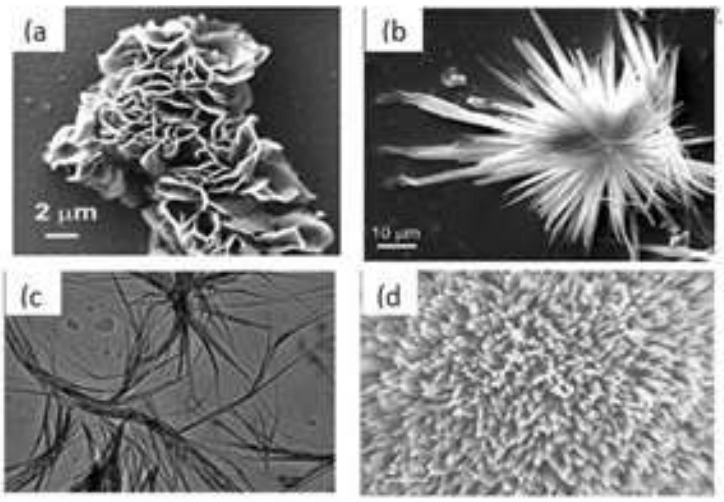


**Figure 6:** FESEM images of dried self-assemblies of 18β-glycyrrhetinic acid (a) α-onocerin (b), betulinic acid (c), betulin (d).

The triterpenoid lupeol (**12**) consisting only one polar –OH group and rigid hydrocarbon backbone with molecular length 1.35 nm isolated from Bombax ceiba is enable to yield supramolecular gel thorough molecular self assembly[23]. Characterization of self- assemblies confirmed that this molecule gives fibrillar morphologies (7a,b). Dihydroxy triterpenoid uvaol **(13**) extracted from different parts of several plants like Plumeria rubra, Olea europaea, Nerium oleander etc. Ghorai et al., reported that this nano sized (1.41 nm) molecule spontaneously self-assembled in various neat organic solvents or aqueous organic binary solvent mixtures to produce nano to micro level garland, flower, and petal-like porous supramolecular structures (Fig.7c)[24]. Similarly the isomer of uvaol, oleane type dihydroxy pentacyclic triterpenod erythrodiol (**14**) with molecular size 1.57 nm isolated from leaves of *Olea europia*, yields micro-sized flowers and grass like morphologies (Fig. 7d) along with nanosized fibrillar network [25].

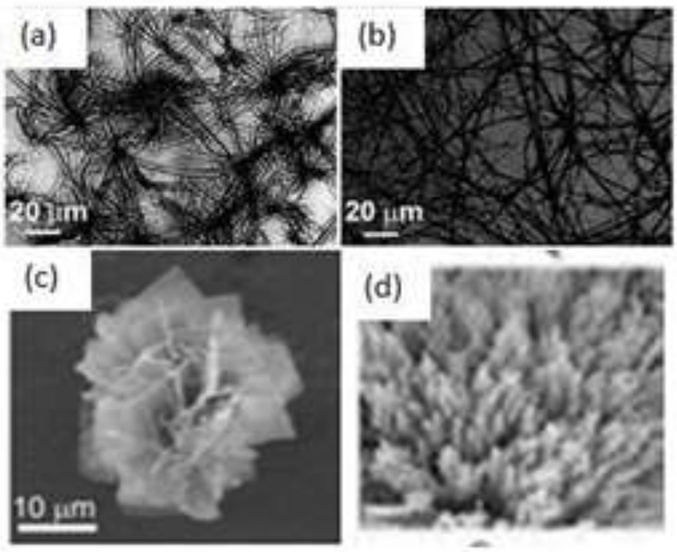


**Figure 7:** FESEM images of lupeol (a,b), uvaol (c) and erythrodiol (d).

2. **Derivatives of terpenoids:** Derivatives of some of the above discussed terpenoids have prepared and their self-assembly property also been studied. Derivatives are generally developed by reactions at hydroxyl group or carboxylic acid group. The reasons behind the preparation of such derivatives are (i) to increase the non covalent force of attraction so that they can build a supramolecular assembly system, (ii) to increase the solubility in aqueous solvent which is known as green solvent.

Bag et al., have synthesized a series of esters of arjunolic acid (Fig.8a) and studied self-assembly property in different neat organic solvents. All the derivatives are excellent supramolecular gelator and they yields fibrillar network by self-assembly[26]. They also revealed that with increasing the chain length in esters gelation ability increase and yields strong gel even in alkane solvents. P-nitro benzyl ester produces gels in most solvents especially in aromatic solvents and also exhibit right-handed helical ribbons in some solvents confirming the chiral aggregation of triterpene chiral skeleton.

Conjugated benzaldehyde and 3,5 dinitro benzyl of methyl arjunolate (Fig.8b) spontaneously self-assembled to give a strong gel in chlorinated alkanes and alcohols and produces micro sized fibrous network[6]. Bag et al reported thermo-reversible organogel based upon donor acceptor interaction of anthrecene derivative (Fig.8c) with trinitrophenol. The morphology of this bimolecular gel includes fibers and vesicles[6].

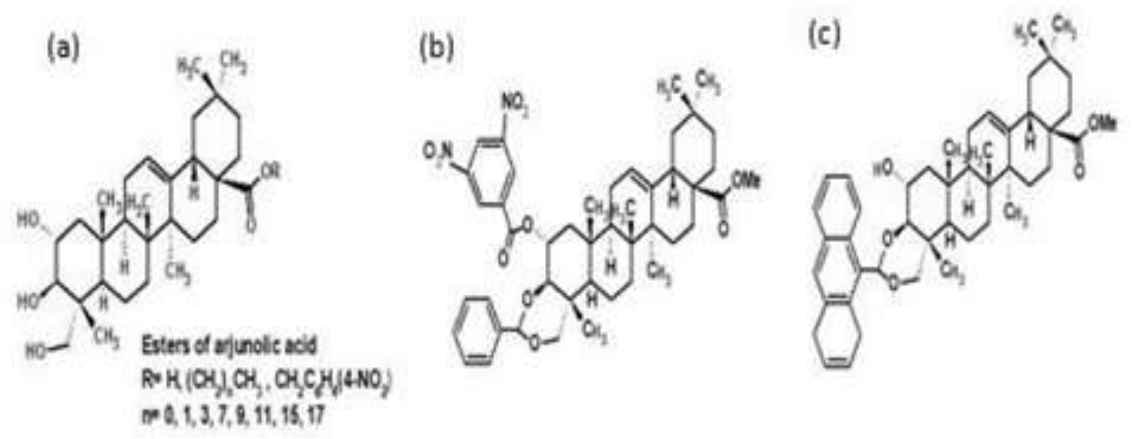


**Figure 8:** Derivatives of arjunolic acid

Sodium salt of glycyrrhetinic acid and sodium and potassium both salts of several triterpenoids like oleanolic acid, corosolic acid, maslinic acid, arjunolic acid and betulinic acid have synthesized. Most of the synthesized salts are excellent gelator and some of them are also hydrogelator. Self-assembly studies of these synthesized salts revealed that except the salts of betulinic acid all are spontaneously self-assembled in several neat and aqueous organic binary solvent mixtures to yield nano to micro level vesicular superstructures. Salts of betulinic acid produce hydrogel with fibriilar network[6,7].

3. **Driving Force and mechanism of self-assembly:** Generally for the molecular self-assembly process the non covalent interactions like hydrogen bonding, electrostatic interaction, pi-pi interaction and vander Waal attractive and repulsive interactions are mainly liable. Terpenoids are consist of lipophilic hydrocarbon back bone with polar functional groups like –OH, -COOH etc. The lipophilic hydrocarbon backbone supports the terpenoid molecules to assemble via dispersion interaction (Fig.8a I); on the other hand the polar functional groups help to form dimer of the terpenoids through H-bonding or electrostatic interactions (Fig.8a II)[7]. A schematic representation is given below (Fig. 8b) to show the probable path way of formation of different supramolecular morphologies even formation of strong gel by molecular self-assembly.

## III. APPLICATIONS

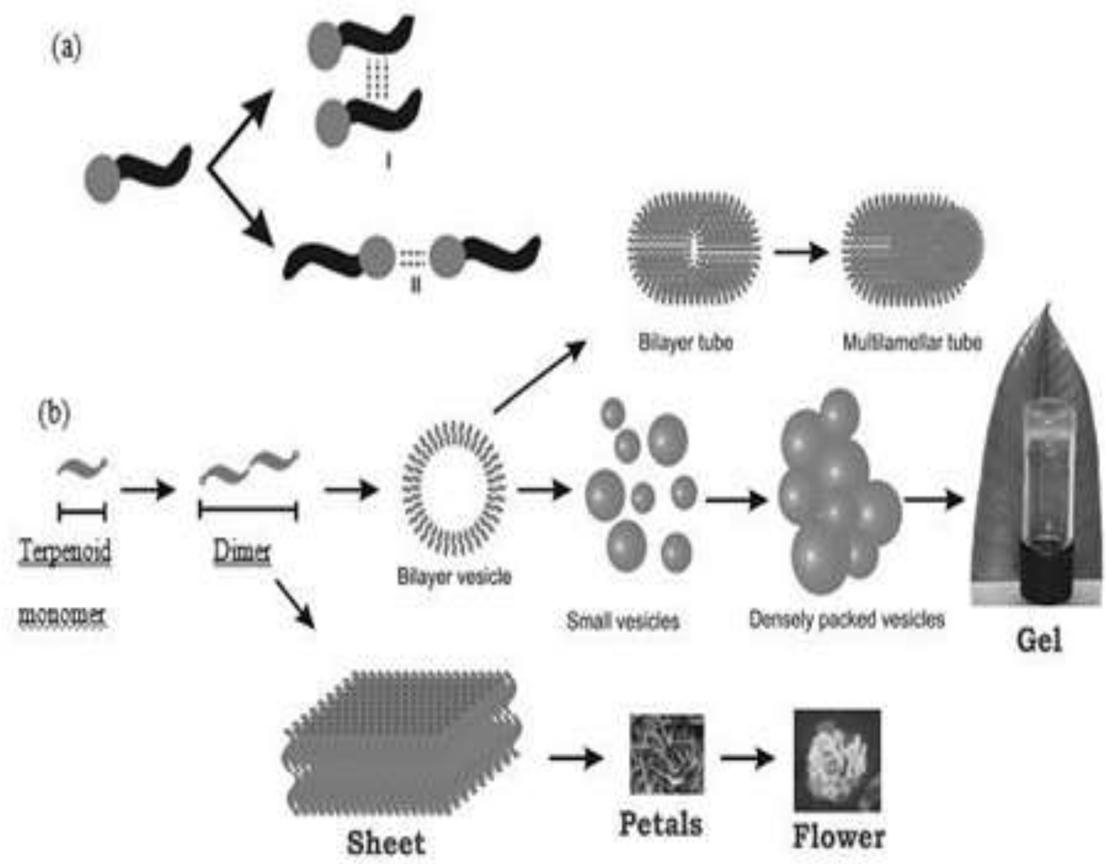


**Figure 9:** Schematic representation of formation of different supramolecular morphologiesby molecular self assembly18.

Terpenoids not only play vital role for growth, development and protection of plants these are important raw materials for food, pharmaceutical and cosmetic industries. The self-assemblies of terpenoids can entrap fluorophores and also been utilized for drug delivery, removal of toxic dyes and pollutants.

## IV. APPLICATION OF SELF-ASSEMBLIES

Deliver of drugs into the targeted cells through biocompatible nano carrier and their controlled release at physiological conditions have gained significant attentipon in recent research investigations. Vesicular morphologies of the terpenoids contain sufficiently large void space inside it and capable to capture several fluorophores along with different drugs. The release of these substances from the vesicles also been demonstrated. The vesicular self-assemblies of diterpenoids **1** and **2** are able to entrap several fluorophores like cationic Rho-B, crystal violet (CV) and anionic 5,6-carboxyfluorescein (CF) including anticancer drug doxorubicin inside them. Release of the drug is also confirmed by addition of membrane-disrupting agent Triton X-100 or by changing the pH of the medium[12,13]. Similarly the vesicular assemblies of triterpenoid **3-7** are also been utilized for entrapment and release of drugs (Fig. 10).

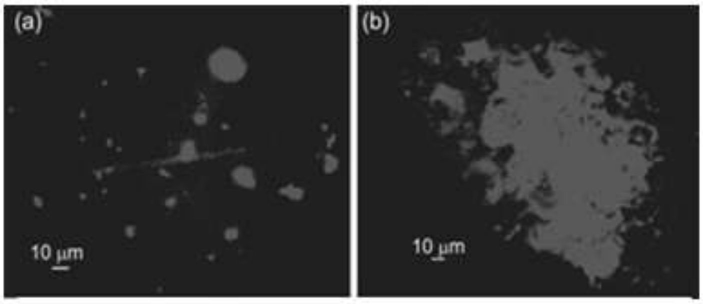


**Figure 10:** Epifluorescent microscopy images of Rho-B loaded selfassemblies of 6 (a)before and (b) after the treatment of Triton-X 100.

Toxic dyes and pollutants have a major responsibility for pollution, so removal of such materials is most important to build a sustainable environment[26]. The porous superstructures like fibers, petals or flowers by self-assembly of terpenoids have large surface area where they can adsorb dyes and pollutants. The flower like self-assemblies of triterpenoid **11** can adsorb several toxic dyes such as Rho-B, Rho-6G, crystal violet, methylene blue, cresol red from their aqueous solution[22]. Recently it is reported that the gel obtained by fibrillar self-assembly of triterpenoid **12** can remove pigments Rho-B and CF from aqueous solution through adsorption. The self-assemblies of this compound is also able to remove heavy metal ion Cr(VI) from contaminated water[23].

The self-assemblies of terpenoids not only used to remove pollutants or drug encapsulation, indeed these self assemblies can mitigate the cytotoxicity induced by drugs in human healthy cells. The self-assemblies of **5** can reduce the cytotoxicty induced by doxorubicin in human healthy peripheral blood mononuclear cells (hPBMCs) and protected the cells by inhibiting inflammatory pathways generated by DOX treatment[27]. The assemblies of sodium and potassium salts of **5** along with assemblies of **5,** can exhibit antileukemic efficacy. Among the three assemblies the sodium salt of **5** showed better effect. The assemblies interact with extrinsic and intrinsic apoptotic proteins of leukemic cells and killed those cells by inducing apoptotic pathways[28].

## V. APPLICATION OF TERPENOIDS IN FOOD INDUSTRY

Terpenoids are the main ingredients of essential oils for which plants offer a broad range of pleasant smells like flowery, fruity, woody or balsamic. Generally the mono terpenoid and sesquiterpenoids have such scents for which terpenoids are serving as important class of compounds for flavor and fragrance. Hence these compounds are exploited in food and cosmetic industries. Essential oils extracted from leaves, flowers and fruits of plants contain high percentage of monoterpenes and give flowery or fruity smells. Sesquiterpenoids are main constituent of woody oils which has woody or balsamic odours. Many of these compounds can exist in different enantiomeric forms and they differ by either smell sensation or smell intensity[29]. Few examples of terpenoids used as flavouring agents in industry with their source and odour are given in table 1.

**Table 1: List of few terpenoids used in food industry**

| Sl.No | Name of terpenoid | Source | Odour | Use |
|---|---|---|---|---|
| **1.** | Menthol | Menthaarvensis | Minty | chewing gum, cigarette |
| **2.** | Menthone | Pelargonium geraniums | Minty, Peepermintlike | confectionariesor beverages |
| **3.** | D-Carvone | Carum carvi | Spicy and breadlike | millennia in food |
| **4.** | D-limonene | citrus species | Orange peel | foods, beverages and chewing gum |
| **5.** | Citral | Cymbopogon citrates | Lemon peel | beverages |
| **6.** | 1,8 Cineole or Eucalyptol | Eucalyptus globules | camphoraceou scool | baked goods, confectionery, meat products and beverages |
| **7.** | Linalool | Coriandrum sativum L | floral, petitgrainlike, woody and lavender like | beverages, candy, ice cream and baked goods |
| **8.** | Safranal | Crocus sativusL | saffron, dried hay like | Foodstuff |

## VI. APPLICATIONS OF TERPENOIDS IN PHARMACEUTICALS

In recent years, the terpenoid molecules has gained more attention and make a significant position in the field of medicine due to its several biological activities like anticancer, anti-inflammatory, antibacterial, antiviral, antimalarial, antidiabetic, promoting the transdermal absorption, preventing and treating cardiovascular diseases etc. Therefore the research investigation on biological activities of terpenoids will provide development of new drugs as well as improves the methods of treatment. Most of the terpenoids showing biological activities are isolated from the medicinal plants such as a mono terpenoid perillyl alcohol isolated from the essential oils of lavender, peppermint etc. have been utilized as anticancer agent. Another monoterpenoid Paeoniflorin extracted from root of Paeonia lactiflora exhibit anti-inflamatory effect[30]. Sesquiterpenoid Patchouli alcohol acts as antibacterial agents. Table 2 shows various examples of terpenoids which can exhibit several biological properties and have medicinal importants.

**Table 2:** Terpenoids exhibit biological activities

| Sl. No | Classification | Name of terpenoid | Source | Biologcal activity | Reference |
|---|---|---|---|---|---|
| **1.** | Mono terpenoid | Geraniol | rose oil, citronella, lemongra ss etc. | Broad spectrum of anti cancer such as Antilung cancer, colon cancer, prostate cancer, pancreatic cancer, and liver cancer | 30 |
| **2.** | Sesqui terpenoid | Costunolide | Aucklan dia lappa | Antileukemia, melanoma,colon cancer etc. | 30 |
| **3.** | Diterpenoid | Paclitaxel | taxus plants | ovarian cancer and breastcancer | 30 |
| **4.** | Triterpenoid | ursolic acid | Plumeria rubra | Antiliver cancer, breast cancer, osteosarcoma etc. and also shows anti-HIV activity | 30 |
| **5.** | Monoterpe noid | Limonene | citrus species | Exhibit antiinflammatoryanti-tumor activity | 31 |
| **6.** | Sesquiterp enoid | IVSE | Inula japonica | Exhibit antiinflammatory activity | 30 |
| **7.** | Sesquiterp enoid | Triptolidenol | Tripteryg ium wilfordii | treat various autoimmune and inflammation-related disorders | 30 |
| **8.** | Sesquiterp enoid | Farnesol | Lemon grass | Anticancer activity | 31 |
| **9.** | Diterpenoid | Andrograph olide | Androgra phis paniculata | Antibacterial activity towards P. aeruginosa and Staphylococcus aureus,also shows antiviral effect to f the chikungunya virus (CHIKV) | 30 |
| **10.** | Triterpenoid | Oleanolic acid | Lantana camara | Inhibitory effect on S. aureus and Streptococcus mutans and also exhibitanti-HIV activity | 30 |
| **11.** | Triterpenoid | Betulinic acid | Ziziphus jujuba | anti-HIV activity | 30 |

| | | | | | |
|---|---|---|---|---|---|
| **12.** | Diterpenoid | Putranjivain A | Euphorbia jolkini | antiviral effect againstHSV-2 | 30 |
| **13.** | Triterpenoid | moronic acid andbetulonic acid | Rhus javanica | inhibitory effect on HSV-1 | 30 |
| **14.** | Sesquiterpenoid | Artemisinin | Artemisia annua | antimalarial drug | 30 |
| **15.** | Diterpenoid | Tanshinone IIA | Salvia miltiorrhiza | Treating cardiovascular disorders | |
| **16.** | Triterpenoid | Corosolic acid | Psidium guajava | Antidiabetic activity | 32 |
| **17.** | Diterpenoid | Stevioside | Stevia rebaudiana | antihyperglycemic effect | 30 |
| **18.** | Sesquiterpenoid | Nerolidol | ginger, jasmine, neroli, tea tree etc. | Promote transdermal absorption | 30 |
| **19.** | Monoterpenoid | Menthone | Pelargonium geraniums | Promote transdermal absorption | |
| **20.** | Sesquiterpenoid | Elemene | Curcuma wenyujin | Anticancer and anti-inflammatory activity | 31 |

## VII. CONCLUSION AND FUTURE PERSPECTIVE

Secondary plant metabolites are metabolites as produced by plants and hence they are renewable in nature. These play an important role for the development of sustainable society as they exploited in various fields like medicine, food, cosmetic etc. Terpenoids are the major part of secondary plant metabolites which are nano sized. For the presence of lipophilic hydrocarbon backbone along with polar functional groups terpenoids are suitable candidate to yield several supramolecular architectures like vesicles, fibers, tubes, petals, flowers etc. by means of molecular self-assembly. The self-assemblies especially vesicular morphologies are able to entrap fulorophores and can be utilized as nano carriers for targeted drug delivery system. The gels produced by self-assemblies also been utilized to remove toxic dyes, pollutants and heavy metal ions from the contaminated water. These self-assemblies exhibit biological activities like mitigate cytotoxicity in healthy cells induced by drugs as well as antileukemic activity. Indeed the terpenoids are exploited in several industries like food and cosmetic and health care products as flavouring agent for its pleasant smell. Terpenoids also exhibit various biological activities like anti-tumor, antimalaria, anti-viral, anti-inflamotry, antidiabetic etc. so that providing opportunities to utilize them as natural drugs or as ingredients of drugs. Hence it can be concluded that the research investigation on terpenoids provide a broad prospect and economic benefit to build a sustainable society.

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