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Physicochemical Properties of Bioactive Compounds in Ethanolic Extracts of *Achillea santolina* L.: A Review

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Abstract **Review Article**

Achillea santolina L. is a medicinal plant adapted to arid and semi-arid environments and is distinguished by a chemically diverse secondary metabolite profile. Recent research has increasingly highlighted the importance of physicochemical characterization of plant-derived bioactive compounds as a prerequisite for understanding their functional behavior. Ethanolic extraction, owing to its intermediate polarity and amphiphilic nature, represents an effective approach for isolating structurally diverse polar and semi-polar constituents from *A. santolina*. This review presents a comprehensive physicochemical synthesis of current knowledge on the composition of *A. santolina* ethanolic extracts, with a particular emphasis on flavonoids, phenolic acids, and terpenoid constituents. The analysis demonstrates that molecular structure, polarity, lipophilicity, hydrogen-bonding capacity, and electronic conjugation are key determinants governing extraction efficiency, chemical stability, and molecular interactions. Additionally, solvent polarity, ethanol–water ratio, and extraction parameters are shown to have a decisive influence on compound integrity and compositional balance. From an analytical perspective, this review argues that many reported functional properties of *A. santolina* extracts are more consistently interpreted through structure–property relationships rather than purely descriptive bioactivity observations. Accordingly, the integration of quantitative physicochemical descriptors with advanced analytical and computational approaches is proposed as a critical step toward improving mechanistic understanding, reproducibility, and comparability in future studies of *A. santolina* and related medicinal plants.

Keywords: *Achillea santolina*; Ethanolic extraction; Physicochemical properties; Bioactive compounds; Flavonoids.

1. INTRODUCTION

Medicinal plants constitute a major reservoir of structurally varied chemical entities whose biological and functional relevance is fundamentally regulated by their physicochemical properties. Within this context, plants of the genus *Achillea* (Asteraceae) have received substantial scientific interest due to their rich secondary metabolite composition and proven ethnobotanical usage [1] . *Achillea santolina* is a perennial aromatic herb characterised by silver-grey foliage and yellow inflorescences (Figure 1) . It is a perennial xerophytic species adapted to arid and semi-arid environments, ecological conditions that are often associated with the accumulation of chemically stable and functionally versatile metabolites. These combined characteristics—chemical richness, environmental adaptation, and documented traditional use—render *A. santolina* a suitable and relevant model for investigating the physicochemical behaviour of bioactive plant constituents [2].

From a chemical perspective, the biological potential of *A. santolina* cannot be adequately interpreted without a detailed understanding of the physicochemical properties of its bioactive constituents. Key parameters such as molecular weight, polarity, lipophilicity, hydrogen-bonding capacity, and electronic distribution critically influence extraction behaviour, solubility, chemical stability, and interactions with biological systems. The physicochemical framework supplies a mechanistic explanation by linking molecular structure to functional performance, offering a more unified and in-depth approach than descriptive assessments of biological activity [3] .

Ethanolic extraction has emerged as one of the most widely employed techniques in phytochemical investigations of *A. santolina*. Ethanol is characterised by an intermediate dielectric constant and amphiphilic nature, enabling effective solubilization of both polar and semi-polar compounds [4]. These qualities permit the extraction of flavonoids, phenolic acids, and a fraction of terpenoid compounds, generating chemically complex extracts that reflect the plant's metabolite diversity [5]. Solvent-solute interactions in ethanol are regulated by hydrogen bonds, dipole-dipole interactions, and van der Waals forces. The ethanol–water ratio provides an adjustable polarity that affects extraction selectivity [6].

Although numerous studies have reported the biological activities of *A. santolina* extracts, comparatively fewer investigations have systematically addressed the underlying physicochemical principles that govern these effects. This gap underscores the need for a review that emphasises structure–property relationships and extraction chemistry rather than isolated biological endpoints. Therefore, the present review focuses on the physicochemical properties of bioactive constituents in ethanolic extracts of *A. santolina*, integrating available analytical and chemical evidence to provide a coherent and rigorous synthesis that supports future physicochemical, biophysical, and computational investigations.

Figure 1:. *Achillea santolina* plant showing characteristic silver-grey foliage and yellow inflorescences. Field photograph (authors)

2. Physicochemical framework of ethanolic extraction

The physicochemical compatibility between solvent qualities and the molecular properties of target compounds greatly impacts the efficacy and selectivity of phytochemical extraction. In this sense, ethanol represents a solvent system of particular interest due to its intermediate dielectric constant (ε = 24.3 at 25°C), which positions it between highly polar aqueous systems and non-polar organic solvents [7]. This physicochemical characteristic enables ethanol to accommodate a large range of secondary metabolites exhibiting varying polarity and lipophilicity values [8]. Ethanolic extraction benefits from dipole moments, hydrogen bonds, and dispersion forces that enhance solvent-solute interactions [9]. Ethanol readily dissolves phenolic acids and flavonoids, which typically possess low to moderate log P values and multiple hydroxyl groups, due to its effective hydrogen-bond donor and acceptor properties [10]. Terpenoids, with their higher log P values and lower polarity, are solubilised predominantly by van der Waals contacts and partial polarity matching, rather than hydrogen bonding (Figure 2).

The ethanol–water ratio provides an adjustable polarity gradient that critically affects extraction selectivity. By increasing the dielectric constant of the solvent, a higher water content enhances the extraction of polar phenolic compounds with low log P values [11]. Solvent polarity impacts extract composition, consequently altering physicochemical characterisation [12]. Extraction kinetics depend on temperature, time, and plant matrix [13]. Elevated temperatures promote solute diffusivity and solubility by reducing solvent viscosity and altering cell structures, but can also accelerate degradation [14]. Optimising ethanolic extraction demands balancing mass transfer with molecular integrity to produce repeatable and chemically consistent *A. santolina* extracts [15].

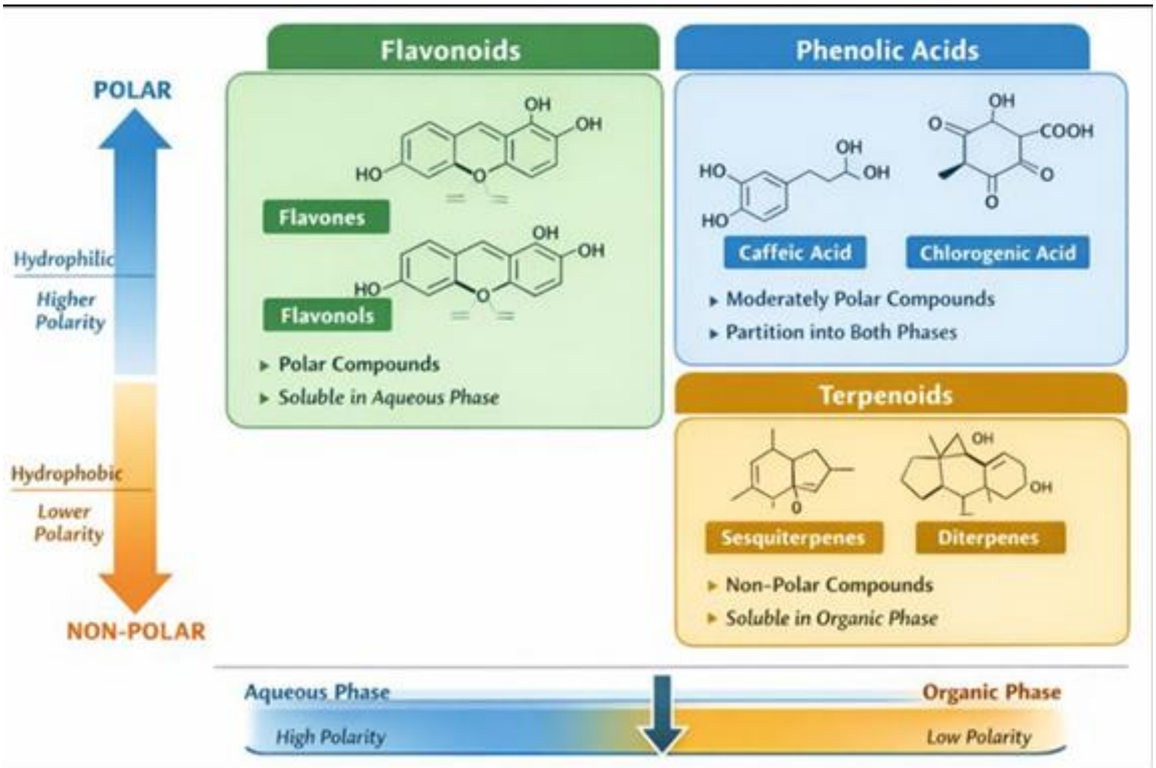

Figure 2: Major types of bioactive components in ethanolic extracts of *Achillea santolina*, adapted from Wink, 2015 [16]

3. Chemical classes of bioactive compounds in *A. santolina*

Studies have shown that the *A. santolina* plant has a complex chemical composition with secondary metabolites whose physical and chemical properties affect their extraction and functions [17]. The ethanolic extracts of the plant are characterised by their richness in phenolic, flavonoid, and terpenoid compounds [18], due to the ability of the intermediate polar ethanol to dissolve chemically diverse molecules (Figure 3).

3. 1. Flavonoids

Flavonoids are an important class of bioactive compounds found in ethanolic extracts of *A. santolina*. The physically distinctive C6–C3–C6 backbone of flavonoids is formed by a heterocyclic pyran ring joining two aromatic rings [19]. Among the special physicochemical properties that this conjugated system offers are redox activity, UV–visible absorbance, and the ability for π–π interactions [20]. The polarity and hydrogen-bonding capacity of the flavonoid skeleton are enhanced by the addition of hydroxyl groups at different locations, which makes the molecule more soluble in ethanolic solution [21]. The lipophilicity of flavonoid aglycones is generally low, but the polarity and aqueous affinity of glycosylated derivatives are higher[22]. Electronic delocalisation across the conjugated system contributes to the relative chemical stability of flavonoids, particularly under mild extraction conditions [23]. However, excessive heat or prolonged exposure to light may promote oxidative degradation, emphasising the importance of controlled extraction parameters [24]. The physicochemical versatility of flavonoids underlies their frequent association with diverse biological effects, although such effects ultimately depend on structure–property relationships rather than mere presence [25].

3. 2. Phenolic Acids and Related Polyphenols

Phenolic acids constitute another major fraction of *A. santolina* ethanolic extracts. These compounds are generally characterised by a phenolic ring bearing one or more hydroxyl groups and a carboxylic acid functionality, conferring acidic behaviour and strong hydrogen-bonding potential [26]. The ionisation state of phenolic acids is highly dependent on pH, which in turn influences solubility, stability, and interaction with solvent molecules [27]. In ethanolic extraction systems, phenolic acids are effectively solubilised through a combination of hydrogen bonding and dipole–dipole interactions [28]. Their relatively low molecular weight and polar surface area favour diffusion from the plant matrix into the solvent phase [29]. From a physicochemical perspective, the redox-active nature of phenolic acids is closely related to their electron-donating hydroxyl groups and resonance stabilisation of phenoxyl radicals [30]. The stability of phenolic acids during extraction is generally high. However, esterified or highly substituted derivatives may undergo hydrolysis or rearrangement under unfavourable conditions [31]. Consequently, understanding the chemical environment during extraction is essential for preserving the native physicochemical profile of these compounds.

3. 3. Terpenoids

Ethanol extracts from the *A. santolina* plant contain terpenoids, especially monoterpene and triterpene derivatives, which are more lipophilic than phenolic compounds. Terpenoids are composed of isoprene units and vary in molecular weight, degree of unsaturation, and functional substitutions, resulting in diverse physicochemical behaviours [32]. Although nonpolar solvents readily extract terpenoids, ethanol dissolves large quantities of oxidised terpenoids due to its polarity and dispersion reactions[33]. Their lipophilic nature enhances their interaction with biological membranes, influencing their mechanism of action[34]. Volatility and oxidizability are important physicochemical properties of terpenoids [35]. Loss of volatile components or oxidative modifications during extraction and storage can significantly alter the chemical composition of ethanolic extracts. Therefore, during extraction, light, air, and heat must be minimised to obtain an extract rich in terpenoids [36].

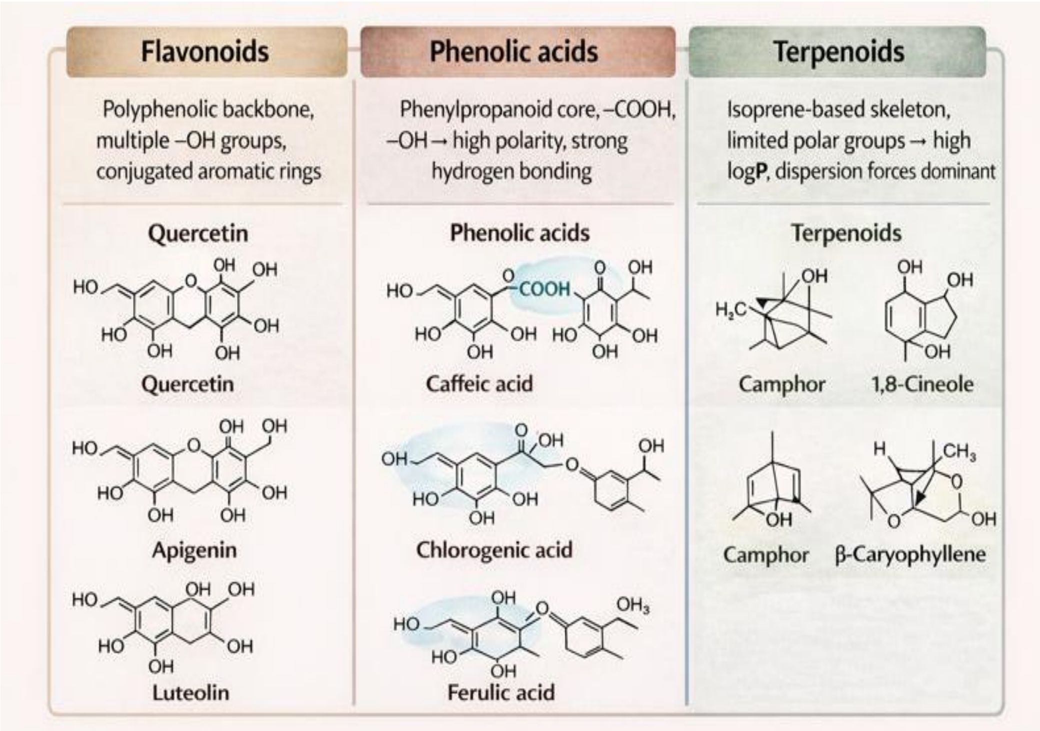

Figure 3: Typical chemical structures: Flavonoids, phenolic acids, and terpenoids in ethanolic extracts of *A. santolina* (authors' depiction based on literature data)

4. Structure–property relationships

The functional performance of bioactive constituents in ethanolic extracts of *A. santolina* is closely governed by structure–property relationships that determine solubility, stability, diffusivity, and molecular interactions . These relationships provide a mechanistic framework for understanding both extraction efficiency and subsequent biological behavior [37] . Molecular weight is a primary factor influencing diffusional mobility and solvent accessibility. Low- to medium-molecular-weight phenolic compounds generally diffuse more readily into ethanolic media, whereas larger or highly substituted molecules may exhibit limited extraction efficiency due to steric constraints . Polarity and lipophilicity, commonly expressed through partition coefficients (log P), further modulate solvent affinity and membrane interaction potential [38]. Hydrogen-bonding capacity represents another critical determinant of physicochemical behavior. Compounds bearing multiple hydroxyl groups readily form hydrogen bonds with ethanol, enhancing solubility while potentially limiting passive membrane permeability . In contrast, more lipophilic molecules with fewer polar functional groups tend to exhibit stronger membrane partitioning but reduced solubility in polar solvents [39].

Electronic structure also contributes significantly to molecular stability and reactivity . Conjugated aromatic systems enable electron delocalization, which enhances chemical stability and redox activity. This feature is particularly evident in flavonoids and phenolic acids, where resonance stabilization supports both antioxidant function and resistance to spontaneous degradation [40]. Collectively, these structure–property relationships highlight the importance of detailed chemical characterization when evaluating ethanolic extracts . Rather than viewing such extracts as uniform mixtures, a physicochemical perspective reveals them as dynamic assemblies in which overall behavior arises from the integrated contributions of individual molecular structures [41].

5. Biophysical and molecular interaction mechanisms

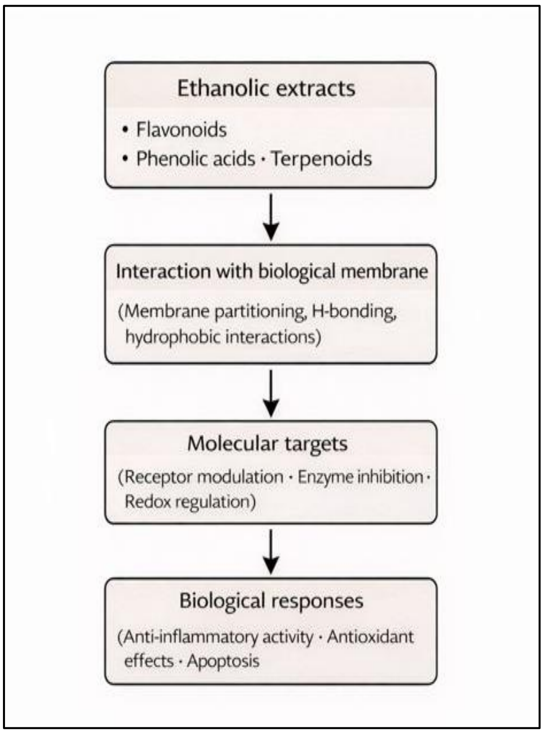

Figure 4: Conceptual flowchart illustrating interactions between *Achillea santolina* ethanolic extract bioactive constituents, molecular targets, and biological responses via membrane interactions (Authors' illustration based on literature data)

At the molecular level, the interaction of *A. santolina* bioactive constituents with biological systems is governed by physicochemical principles such as membrane affinity, electrostatic interactions, and thermodynamic favorability. Lipophilic terpenoids tend to partition into lipid bilayers, potentially altering membrane fluidity and permeability [42] . This effect is strongly influenced by molecular size, degree of unsaturation, and functional group composition (Figure 4) . Phenolic compounds and flavonoids, by contrast, often interact with membrane surfaces or protein targets through hydrogen bonding and π–π stacking interactions . Such interactions are reversible and highly dependent on environmental conditions, including pH and ionic strength [43] . The ability of these compounds to chelate metal ions or modulate redox processes further reflects their underlying chemical structure . From a biophysical standpoint, the free energy of interaction between bioactive molecules and biological targets determines the strength and specificity of binding [44] . Ethanolic extracts, containing a mixture of compounds with varying affinities, may exhibit synergistic or antagonistic effects that cannot be predicted solely from individual constituents. This complexity highlights the value of physicochemical modeling and computational approaches in future investigations.

6. Stability and physicochemical constraints of ethanolic extracts

The physicochemical stability of ethanolic extracts of *A. santolina* is a key factor affecting their chemical integrity and reproducibility . Stability is influenced by both intrinsic molecular properties and external conditions during extraction and storage . Phenolic compounds and flavonoids generally show good stability due to conjugated aromatic systems; however, their multiple hydroxyl groups increase susceptibility to oxidative degradation under heat, light, or oxygen exposure . Oxidation disrupts conjugation, leading to structural changes and reduced functional activity [45].

Terpenoids, particularly mono- and sesquiterpenes, present additional challenges owing to their volatility and tendency toward autoxidation, especially under elevated temperature and light . Although ethanol is chemically inert, it can indirectly affect stability by modifying solvent microenvironments and diffusion behavior [46] . Variations in pH, arising from residual water and organic acids, may further influence the ionization and degradation of phenolic acids . Accordingly, controlled extraction conditions, low-temperature storage, protection from light, and limited oxygen exposure are essential to preserve the physicochemical profile and extend the shelf life of *A. santolina* ethanolic extracts [47].

7. Research limitations

Despite increasing studies on the phytochemical composition of *A. santolina*, the physical and chemical interpretation of its ethanolic extracts remains incomplete. Most studies are limited to qualitative characterisation, while quantitative relationships between composition and properties, including distribution coefficients and thermodynamics, remain inadequate[48] . Future research should integrate advanced analytical techniques with computational methods to improve mechanistic understanding and optimise extaction . Greater emphasis should also be placed on the design of the solvent system, particularly the ethanol-to-water ratios, and long-term stability studies to ensure the reproducibility and standardisation of ethanolic *A. santolina* extracts [49, 50, 51].

8. CONCLUSIONS

This review underscores the central importance of physicochemical principles in interpreting the bioactive composition of ethanolic extracts of *A. santolina* . By integrating structure–property relationships with solvent–solute interactions and stability considerations, the work demonstrates that extraction efficiency and functional behavior are not incidental outcomes but direct consequences of molecular architecture and physicochemical constraints . The coexistence of flavonoids, phenolic acids, and terpenoids confers marked chemical diversity, with each class contributing distinct solubility, stability, and interaction characteristics .

From the authors' perspective, ethanol represents a particularly appropriate extraction medium for *A. santolina*, provided that extraction parameters are rationally optimized to preserve molecular integrity and reproducibility. Adopting a physicochemical framework offers a more rigorous and predictive basis for evaluating plant extracts than descriptive bioactivity approaches alone . Future studies that combine quantitative physicochemical descriptors with advanced analytical and computational methods are expected to significantly advance mechanistic understanding and enhance the scientific value of research on *A. santolina* and related medicinal plants .

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