

Review Article

Arzanol, a Potent mPGES-1 Inhibitor: Novel Anti-Inflammatory Agent

Pankaj S. Kothavade, Dnyaneshwar M. Nagmoti, Vipin D. Bulani, and Archana R. Juvekar

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Nathalal Parekh Marg, Matunga, Mumbai 400 019, India

Correspondence should be addressed to Archana R. Juvekar; arj04@rediffmail.com

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Arzanol is a novel phloroglucinol α -pyrone, isolated from a Mediterranean plant *Helichrysum italicum* (Roth) Don ssp. *microphyllum* which belongs to the family Asteraceae. Arzanol has been reported to possess a variety of pharmacological activities. However, anti-inflammatory, anti-HIV, and antioxidant activities have been studied in some detail. Arzanol has been reported to inhibit inflammatory transcription factor NF κ B activation, HIV replication in T cells, releases of IL-1 β , IL-6, IL-8, and TNF- α , and biosynthesis of PGE₂ by potentially inhibiting mPGES-1 enzyme. Diversity of mechanisms of actions of arzanol may be useful in treatment of disease involving these inflammatory mediators such as autoimmune diseases and cancer. This review presents comprehensive information on the chemistry, structure-activity relationship, and pharmacological activities of arzanol. In addition this review discusses recent developments and the scope for future research in these aspects.

1. Introduction

Inflammation is the reaction of living tissue to injury, in which a series of changes of the terminal vascular bed, blood, and connective tissue tends to eliminate the injurious agent and to repair the damaged tissue [1]. Inflammatory process involves evidence of prostaglandins, leukotrienes, histamine, bradykinin, platelet-activating factor (PAF), and interleukins (IL) [2]. Eicosanoids, namely, prostaglandins and leukotrienes, are key substances involved in inflammatory reactions; hence, these eicosanoids inhibition is major target for anti-inflammatory agents. Nonselective cyclooxygenase (COX) inhibitors (Diclofenac, Indomethacin), selective COX-2 inhibitors (Celecoxib, Etoricoxib), phospholipase A₂ (PLA₂) inhibitors (Corticosteroids) and newer therapies such as antitumour necrosis factor (TNF)- α therapy (Etanercept, Infliximab, and Adalimumab), and anti-CD20 therapy (Rituximab) are often used to inhibit the underlying immune process. However, long-term clinical use of these agents is associated with risk of adverse effects, as they have been linked with gastrointestinal toxicity and an increased risk of adverse cardiovascular events. In recent years, researchers are involved in finding new categories of the development of

other enzymatic targets within the arachidonic acid pathway, including the PGE₂ synthase (PGES) to overcome the side effect of existing compounds. Several compounds like MF-63, NS-398, MK-866, and Triclosan are microsomal PGE₂ synthase (mPGES) inhibitors, which were assayed for *in vitro* studies, but some of them have shown poor bioavailability and hepatotoxicity [3].

Helichrysum italicum (Roth) Don ssp. *microphyllum* is mediterranean plant belongs to the Asteraceae family. This plant is widespread in the areas of stony, arid, sandy mediterranean region along the east coast and on the islands of the Adriatic Sea [4]. *H. italicum* has been reported to possess anti-inflammatory, antioxidant [5], antiviral [6], antimicrobial [7], and antifungal activities [8]. An array of phytochemical constituents, namely, α -amyrin, uvaol [9], beta-diketones [10], kaempferol-3-glucoside, naringenin-glycoside [11], gnaphaliin, pinoembrin, tiliroside [12], eudesm-5-en-11-ol [13], *iso*-italicene epoxide, β -costol, (*Z*)- α -*trans*-bergamotol [14], and phloroglucinol α -pyrone arzanol [15], were reported in *H. italicum*.

Appendino et al. [15] started systematic study of phloroglucinol α -pyrone class of compounds which possessed

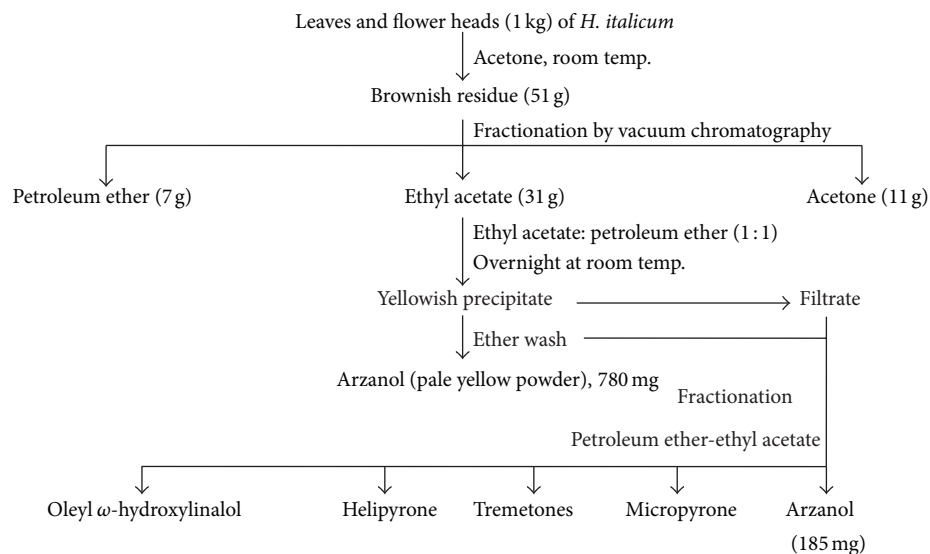


FIGURE 1: Schematic representation of isolation of phytochemical constituents of *H. italicum* subsp. *microphyllum*. (Adapted and modified from Appendino et al. [15].)

anti-inflammatory activity. They developed isolation techniques with high yield of compounds and screened them for anti-inflammatory activity. Arzanol, a prenylated heterodimeric phloroglucinyl pyrone, was firstly identified in early 2007 and detected as a major anti-inflammatory compound. It inhibits NF κ B (nuclear factor kappa B) activation, release of proinflammatory mediators like interleukins (IL), TNF- α , prostaglandin E₂ (PGE₂) [15], and inducible microsomal PGE₂ synthase-1 (mPGES-1) [16]. Arzanol also inhibits HIV-1 replication in T cells; hence it has anti-HIV property [15]. Antioxidant and cytotoxic action of arzanol were studied by [17]. Hence, present review will focus on the isolation, chemistry, and pharmacology of the arzanol.

2. Isolation and Identification of Arzanol

The *H. italicum*, a best known medicinal plant from the Mediterranean area, was used as an anti-inflammatory and anti-infective plant in Greek-Roman system of medicine. Appendino et al. [15] developed an extraction and isolation procedure of arzanol from the acetone extract of aerial parts, mainly leaves and flower heads of *H. italicum*. The acetone extract showed potent NF- κ B-inhibitory activity; in an attempt to identify the active compounds, the acetone extract was separated by solid-phase extraction into three fractions (petroleum ether-ethyl acetate, and acetone). They succeeded in isolating a pale yellow compound with powerful NF- κ B inhibiting activity (IC₅₀ = 5 μ g/mL), superior to that of all the other products obtained by bioassay-directed fractionation of the mother liquors by gravity column chromatography. Approximately 780 mg of arzanol was isolated from the extracts representing 1 kg dried aerial parts, mainly leaves and flower heads of *H. italicum*, as shown in Figure 1 and was identified and characterized by spectroscopic methods [15–18].

3. Chemistry of Arzanol

Arzanol belongs to phloroglucinol α -pyrone category. Structure of arzanol is identical with homoarenol, (Figure 2(a)) which was isolated from *H. arenarium* L. Moench species [19]. Appendino et al. [15] derived the name “arzanol” on the basis of plant *H. italicum* collected from Sardinian village—Arzana.

Arzanol is a prenylated heterodimeric phloroglucinyl α -pyrone chemically known as 3-(3-acetyl-2,4,6-trihydroxy-5-(3-methylbut-2-en-1-yl)benzyl)-6-ethyl-4-hydroxy-5-methyl-2H-pyran-2-one (Figure 2(b)).

3.1. Synthesis of Arzanol (Figure 3) [20, 21]

3.1.1. Step I: Formation of Prenylated Acylphloroglucinol. Phloroacetophenone (i) reacted with *tert*-butyldimethylsilyl chloride (TBDMSCl) for the protection of nonchelated hydroxyls of phloroacetophenone. In presence of prenyl alcohol, tetraphenylporphyrin (TPP) and toluene phloroacetophenone are converted into prenylated acylphloroglucinol (ii).

3.1.2. Step II: Formation of Reactive Methylene-2,4 Dioxypyronone. Acylation of the dianion of ethyl 3-oxopentanoate (iv) with ethyl acetoacetate followed by cyclodehydration lead to formation of α -pyrone (vi). Compound (vi) which reacted with paraformaldehyde gives reactive methylene-2,4 dioxypyronone.

3.1.3. Step III: Desilylation of Prenylated Acylphloroglucinol and Formation of Arzanol. Indirect deprotonation of the phloroacetophenone (iii) by fluoride-induced desilylation using TBAF (tetrabutylammonium fluoride) and mixture of compound (vi) and paraformaldehyde in a warm 40°C chloroform affords arzanol (vii) with yield of 60%.

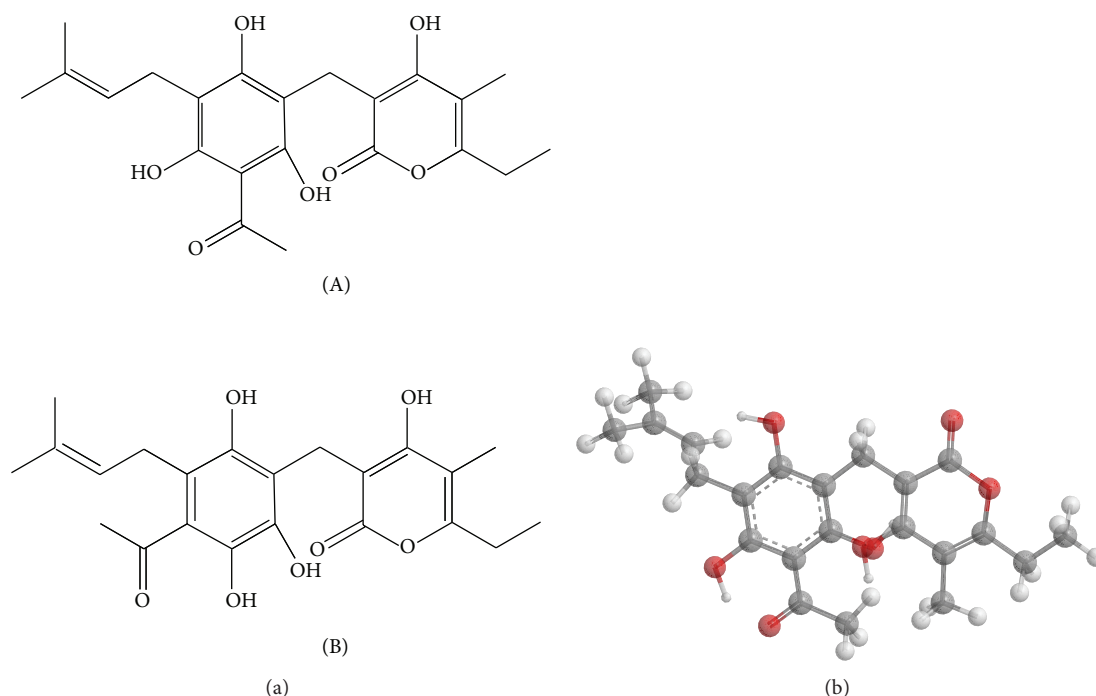


FIGURE 2: (a) Chemical structure of arzanol (A) and homoaranol (B), (b) 3D structure of arzanol: 3-(3-acetyl-2,4,6-trihydroxy-5-(3-methylbut-2-en-1-yl)benzyl)-6-ethyl-4-hydroxy-5-methyl-2H-pyran-2-one.

3.2. *Structure-Activity Relationship (SAR) of Arzanol.* Minassi et al. [21] focussed on the alkylidene linker and pyrone moiety to find out structure activity relationship of arzanol (Figure 4). The pharmacological activity of derivatives of arzanol was assayed using inhibitory potency towards mPGES-1 and 5-LOX.

- In a compound (vii_a) replacement of CH_3 to H at R_2 and R_3 position from pyrone ring does not affect the biological activity.
- Addition of methyl group at R_1 on alkylidene linker (vii_b and vii_c) slightly decreased the activity against mPGES-1 and 5-LOX.
- n-Hexyl residue attached to R_1 (vii_d and vii_e) to analyse the effect of elongated alkyl group leads to beneficial effect. Those compounds have higher mPGES-1 and 5-LOX inhibitory potency over vii_a .
- The benzylidene derivatives (vii_f and vii_g) showed an increased potency towards mPGES-1; hence lipophilic compound at alkylidene linker is beneficial for bioactivity.
- O-alkylation of pyrone moiety ($viii$) have only 5-LOX inhibitory activity and inactive for inhibition of mPGES-1 activity. It suggests that presence of acidic group is responsible for mPGES-1 activity of arzanol.

4. Pharmacological Role of Arzanol in Treatment of Inflammation

Acetophenone, γ -pyrone, and flavonoids have been isolated from the aerial parts of *H. italicum*. 4-Hydroxy-3-(3-methyl-2-butenyl) acetophenone reported inhibitory effect on cyclooxygenase and 5-lipoxygenase, while γ -pyrone glycoside acts as inhibitor of phospholipase A_2 . Flavonoids, namely, gnaphaliin, pinocembrin, and tiliroside, were screened for antioxidant and anti-inflammatory activity. Tilirosides were found to be potent anti-inflammatory flavonoids with respect to Phospholipase A_2 inhibition [5, 12, 22]. Phloroglucinol α -pyrone (Arzanol), an isolated compound from acetone extract of *H. italicum* and have potent mPGES-1 inhibitor activity [16].

Eicosanoid biosynthesis involves various enzymes such as phospholipase, cyclooxygenase (COX), lipoxygenase (LOX), and microsomal PGE_2 synthase (mPGES-1/mPGES-2) enzymes (Figure 5). Phospholipase A_2 activated by some chemical and mechanical stimuli results in release of arachidonic acid from membrane phospholipids. COX-1/COX-2 is responsible for conversion of arachidonic acid to PGG_2 and further into PGH_2 . Prostanoids like PGD_2 , PGE_2 , $PGF_{2\alpha}$, PGI_2 , and TXA_2 are synthesised from PGH_2 in cell-specific manner by PGDS, mPGES-1/mPGES-2, PGFS, PGIS, and TXS enzymes, respectively. LOX is involved in synthesis of leukotrienes (LTA_4 , LTB_4 , LTC_4 , LTD_4 , and LTE_4) [23–25]. Prostanoids, that is, PGI_2 , PGE_2 , and TXA_2 , are derived from COX enzyme. PGI_2 derived from COX-2 plays a role in induction of vasodilatation, inhibition of platelet

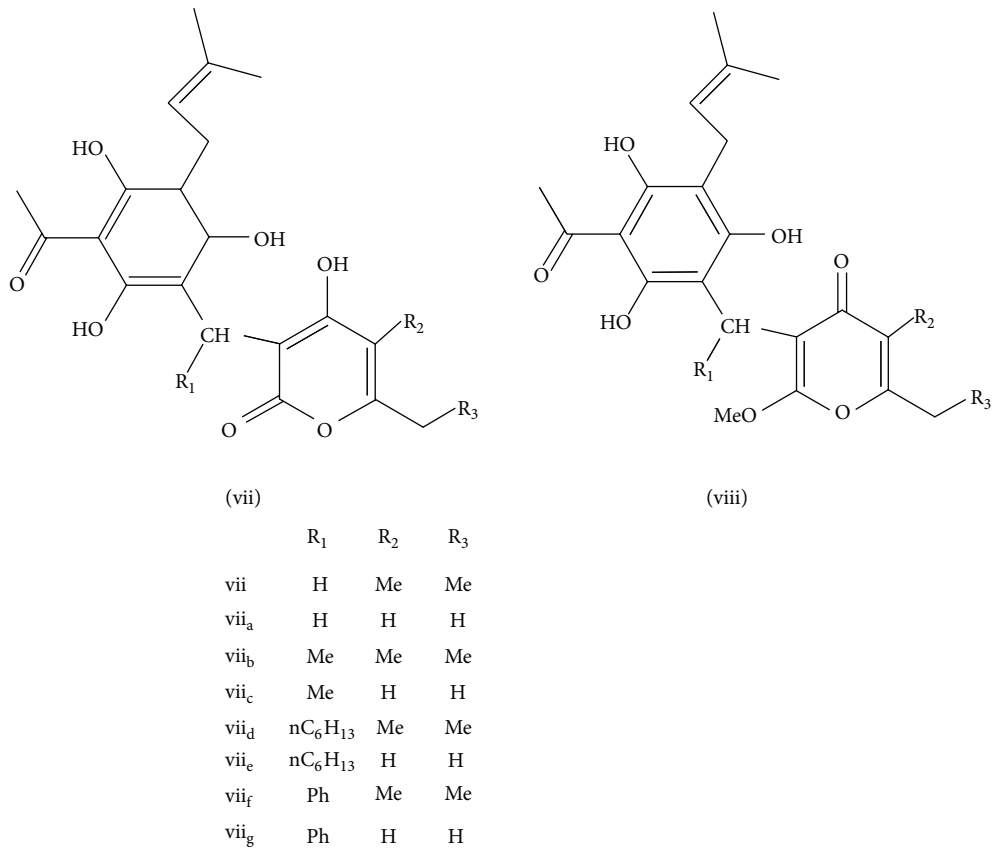


FIGURE 4: Structure-activity relationship of arzanol and its derivatives. (Adapted from Minassi et al. [21].)

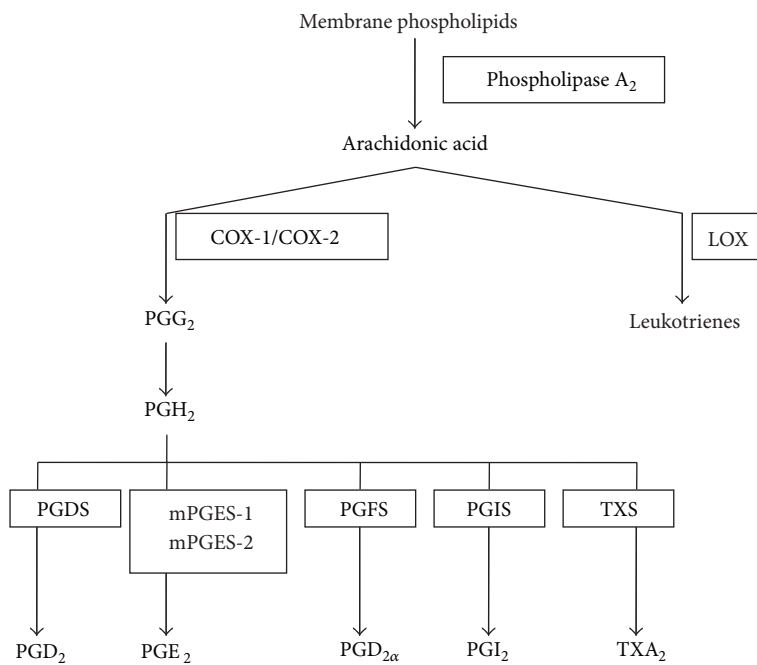


FIGURE 5: Biosynthesis of eicosanoid. (Adapted and modified from Dallaporta et al. [23].)

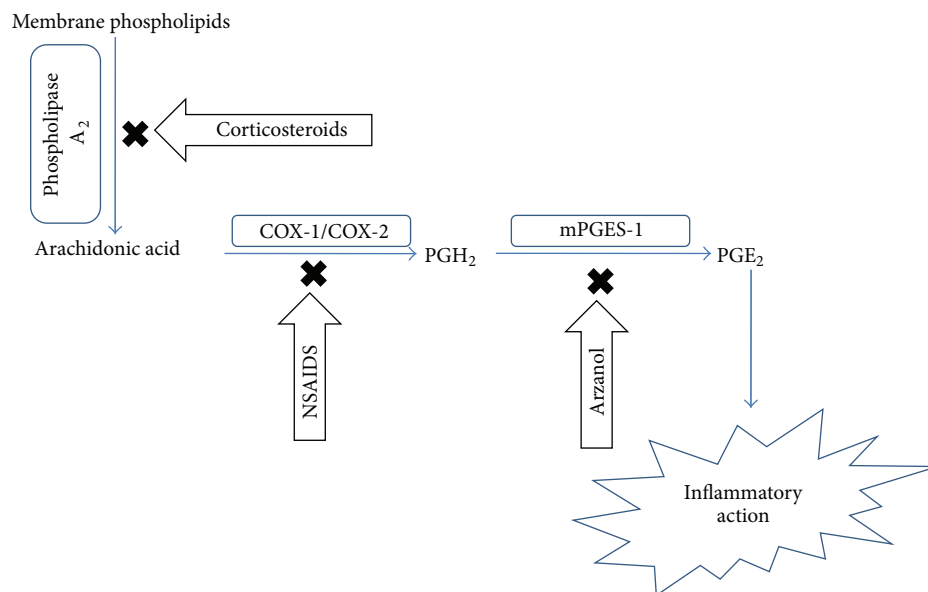


FIGURE 6: Site of action of arzanol and other anti-inflammatory agents.

Figure 6 reflects the site of action of arzanol; it inhibits the mPGES-1 enzyme which plays an important role in conversion of PGH₂ to PGE₂. Formation of PGE₂ in intact human monocytes was determined to evaluate mechanistic activity of arzanol by Bauer et al. [16]. The results showed arzanol could inhibit PGE₂ formation either interference with COX-2 expression or mPGES-1. The mPGES-1 inhibitory activity of arzanol was evaluated by preparing crude mPGES-1 in microsomes of IL-1 β -stimulated A549 cells. Arzanol concentration-dependently inhibited PGE₂ formation having superior over the mPGES-1 inhibitor MK-886 which was used as control. Despite, heat inactivation of microsomal preparations A549 cells for 15 min at 65°C, the nonenzymatic PGE₂ formation was not affected by arzanol. It clearly suggests that arzanol is a specific mPGES-1 inhibitor. Arzanol not only is mPGES-1 inhibitor but also proved as inhibitor of other proinflammatory mediators TXB₂ and leukotrienes by inhibiting 5-LOX and COX-1 enzymes.

In vivo model of acute inflammation for evaluation of arzanol was carried out through carrageenan-induced pleurisy in rats. Arzanol (3.6 mg/kg, i.p.) treatment on carrageenan injected in plural cavity of rats significantly reduces exudate formation (59%), cell infiltration (48%), and inhibition of PGE₂ (47%). However, levels of LTB₄ and 6-keto PGF_{1 α} attenuate to only 31% and 27%, respectively. In conclusion, decreased PGE₂ level may contribute to the inhibition of mPGES-1 by arzanol. Hence, *in vivo* and *in vitro* studies reveal that arzanol is novel eicosanoid inhibitor that importantly acts on PGE₂ synthesis [16].

Previously, arzanol proved as a potent NF κ B inhibitor [15]. NF κ B is involved in activation of large number of genes in response to infections, inflammation, and other stressful situations requiring rapid reprogramming of gene expression [33]. Mechanism of action of arzanol on NF κ B inhibition is explained in later part of this paper.

5. Other Pharmacological Role

5.1. Anti-HIV Activity. Overwhelming immune activation is the main feature of progression of HIV infection. This immune activation manifested by increased B cell activation, T cell turnover, proinflammatory cytokines, and chemokines [34]. Immune activation leads to generation of activated T cell targets for the virus itself, further viral replication process, and host cell transcription and proliferation. Once new CD4⁺ T cells are locally activated and infected, they in turn infect other activated cells, amplifying the initial events [35]. Increasing evidence for cytotoxic T lymphocytes (CTL) in the host defence indicates a protective role against human immunodeficiency virus (HIV) whereas their decline is usually coincident with diseased progression [36].

NF- κ B is one of the key regulators of genes involved in the immune/apoptotic response and is implicated in the regulation of several factors viz. cytokines, chemokines, adhesion molecules etc. Arzanol acts as an anti-HIV-1 agent, by inhibiting NF κ B activation pathway (Figure 7) [15, 37, 38]. TNF- α induced NF κ B activation pathway mediates HIV-1-LTR transactivation in a T cell line. This activated pathway inhibited by arzanol was measured using luciferase enzyme level. Results showed that arzanol inhibited luciferase activity in concentration-dependent manner. The overall effect of arzanol shows it has anti-HIV activity by inhibiting HIV-1 replication in T cells. Plant derived phloroglucinols and synthetically derived dimeric phloroglucinols are also being proved for their anti-HIV activity [39].

5.2. Antioxidant Activity. Oxidation is a process of transfer of electron molecule to an oxidizing substance. Oxidative stress develops due to generation of reactive oxygen species, namely, hydroxyl radicals (OH \cdot) and superoxide anions (O₂ \cdot^- , OOH \cdot) [40]. These radicals are scavenged by

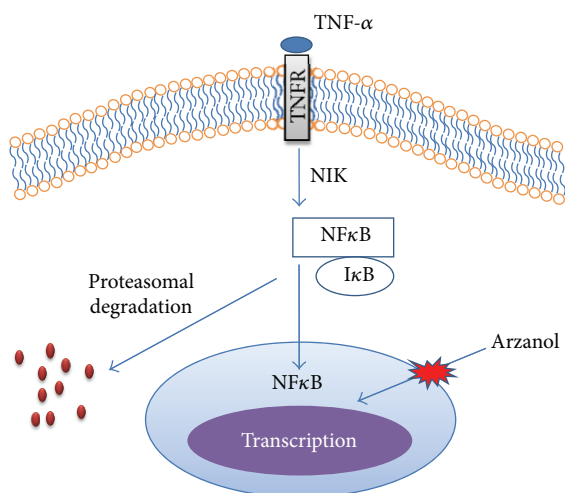


FIGURE 7: TNF- α mediated NF κ B signal transduction pathway. TNF- α bind to TNFR (TNF- α receptor) lead to activation of NF- κ B inducing kinase (NIK) which phosphorylates and activates NF κ B and I κ B (inhibitors of NF κ B) complex. IKK then phosphorylates I κ B, which leads to its ubiquitination and degradation by the proteasome. NF- κ B then enters the nucleus and acts on target genes. Arzanol inhibit this NF κ B activation involved in signal transduction pathway. (Adapted and modified from Appendino et al. [15].)

antioxidants which play an important role in the treatment of diabetes mellitus, inflammatory diseases, atherosclerosis, and carcinogenesis [41].

Rosa et al. [17] investigated antioxidant activity on linoleic acid assay, cholesterol assay, and cell culture method. Linoleic acid autoxidation mediated by FeCl₃, EDTA causes generation of linoleic acid peroxy radicals (LOO[•]). Results show arzanol inhibits this oxidation process completely at 5 nmol while 90% and 45% protection occur at 2.5 and 1 nmol concentration, respectively. Cholesterol degradation and formation 7-keto and 7 β -OH derivatives were significantly inhibited by arzanol (10 nmol) at 1 and 2 h. Oxidative stress in VERO cell line was induced by TBH (*tert*-butyl hydroperoxide) and arzanol showed significant 40% reduction in production of malondialdehyde (MDA). These investigators also proved arzanol is noncytotoxic up to 40 μ M *in vitro* tested in VERO cell culture models [17].

6. Conclusion and Future Perspectives

Arzanol, prenylated heterodimeric phloroglucinyl pyrone, isolated from *H. italicum* subsp. microphyllum. have major anti-inflammatory, antiviral (anti-HIV), and antioxidant activities. Arzanol inhibits NF κ B activation, HIV replication in T cells, releases of proinflammatory mediators like IL-1 β , IL-6, IL-8, and TNF- α , and biosynthesis of PGE₂ by potentially inhibiting mPGES-1 enzyme. Arzanol was widely studied for its pharmacodynamic profile while pharmacokinetic profile still needs to be established. In future, diversity of mechanism of actions of arzanol may be useful in treatment of cancer.

Although, an extensive amount of research work has been done on anti-inflammatory compounds to date, mPGES inhibitors like arzanol are still unknown. Only a few species from genus *Helichrysum* have been investigated [42]. Consequently, a broad field of future research remains possible in which the isolation of new active principles (mPGES-1 inhibitors) from the genus *Helichrysum* would be of great scientific merit.

Abbreviations

COX:	Cyclooxygenase
CTL:	Cytotoxic T lymphocytes
HIV:	Human immunodeficiency virus
IKK:	I κ B kinase
IL:	Interleukins
LOX:	Lipoxygenase
MDA:	Malondialdehyde
mPGES:	Microsomal PGE ₂ synthase
NF κ B:	Nuclear factor kappa B
NIK:	NF- κ B inducing kinase
OVLT:	Organum vasculosum lamina terminalis
PAF:	Platelet-activating factor
PGD ₂ :	Prostaglandin D ₂
PGDS:	Prostaglandin D synthase
PGE ₂ :	Prostaglandin E ₂
PGES:	Prostaglandin E synthase
PGF _{2α} :	Prostaglandin F _{2α}
PGFS:	Prostaglandin F synthase
PGG ₂ :	Prostaglandin G ₂
PGH ₂ :	Prostaglandin E ₂
PGI ₂ :	Prostaglandin I ₂
PGIS:	Prostaglandin I synthase
PLA ₂ :	Phospholipase A ₂
POA:	Preoptic area
TBAF:	Tetrabutylammonium fluoride
TBDMSCl:	<i>tert</i> -Butyldimethylsilyl chloride
TBH:	<i>tert</i> -Butyl hydroperoxide
TNF- α :	Tumour necrosis factor- α
TPA:	Tissue plasminogen activator
TPP:	Tetraphenylporphyrin
TXA ₂ :	Thromboxane A ₂
TXS:	Thromboxane synthase.

Conflict of Interests

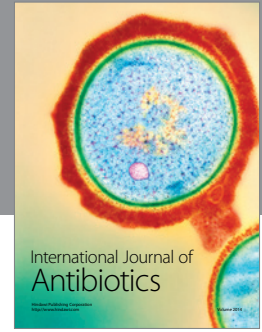
The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] N. Chand and P. Eyre, "Nonsteroidal anti inflammatory drugs: a review. New applications in hypersensitivity reactions of cattle and horses," *Canadian Journal of Comparative Medicine*, vol. 41, no. 3, pp. 233–240, 1977.
- [2] B. Halliwell, J. R. Hoult, and D. R. Blake, "Oxidants, inflammation, and anti-inflammatory drugs," *FASEB Journal*, vol. 2, no. 13, pp. 2867–2873, 1988.

- [3] M. Nakanishi, V. Gokhale, E. J. Meuillet, and D. W. Rosenberg, "MPGES-1 as a target for cancer suppression. A comprehensive invited review 'phospholipase A2 and lipid mediators,'" *Biochimie*, vol. 92, no. 6, pp. 660–664, 2010.
- [4] J. Mastelič, O. Politeo, and I. Jerkovič, "Contribution to the analysis of the essential oil of *Helichrysum italicum* (Roth) G. Don—determination of ester bonded acids and phenols," *Molecules*, vol. 13, no. 4, pp. 795–803, 2008.
- [5] A. Sala, M. del Carmen Recio, R. M. Giner et al., "Anti-inflammatory and antioxidant properties of *Helichrysum italicum*," *Journal of Pharmacy and Pharmacology*, vol. 54, no. 3, pp. 365–371, 2002.
- [6] A. Nostro, M. A. Cannatelli, A. Marino et al., "Evaluation of antiherpesvirus-1 and genotoxic activities of *Helichrysum italicum* extract," *New Microbiologica*, vol. 26, no. 1, pp. 125–128, 2003.
- [7] J. Mastelic, O. Politeo, I. Jerkovic, and N. Radosevic, "Composition and antimicrobial activity of *Helichrysum italicum* essential oil and its terpene and terpenoid fractions," *Chemistry of Natural Compounds*, vol. 41, no. 1, pp. 35–40, 2005.
- [8] A. Angioni, A. Barra, M. Arlorio et al., "Chemical composition, plant genetic differences, and antifungal activity of the essential oil of *Helichrysum italicum* G. Don ssp. *microphyllum* (Willd) Nym.," *Journal of Agricultural and Food Chemistry*, vol. 51, no. 4, pp. 1030–1034, 2003.
- [9] G. Orzalesi, T. Mezzetti, and V. Bellavita, "A new natural triterpenic lactone, alpha-amyryn and uvaol from *Helichrysum italicum* (G. Don)," *Bollettino Chimico Farmaceutico*, vol. 108, no. 9, pp. 540–545, 1969.
- [10] C. G. Casinovi, C. Galeffi, A. Pela, S. Tira, and G. Di Modica, "New beta-diketones from *Helichrysum italicum* G. Don," *Annali dell'Istituto Superiore di Sanita*, vol. 4, no. 3, pp. 186–198, 1968.
- [11] R. M. Facino, M. Carini, L. Franzoi, O. Pirola, and E. Bosio, "Phytochemical characterization and radical scavenger activity of flavonoids from *Helichrysum italicum* G. Don (compositae)," *Pharmacological Research*, vol. 22, no. 6, pp. 709–721, 1990.
- [12] A. Sala, M. C. Recio, G. R. Schinella et al., "Assessment of the anti-inflammatory activity and free radical scavenger activity of tiliroside," *European Journal of Pharmacology*, vol. 461, no. 1, pp. 53–61, 2003.
- [13] A. Bianchini, F. Tomi, P. Richomme, A. Bernardini, and J. Casanova, "Eudesm-5-en-11-ol from *Helichrysum italicum* essential oil," *Magnetic Resonance in Chemistry*, vol. 42, no. 11, pp. 983–984, 2004.
- [14] E. Mancini, L. de Martino, A. Marandino, M. R. Scognamiglio, and V. de Feo, "Chemical composition and possible in vitro phytotoxic activity of *Helichrysum italicum* (Roth) don ssp. *italicum*," *Molecules*, vol. 16, no. 9, pp. 7725–7735, 2011.
- [15] G. Appendino, M. Ottino, N. Marquez et al., "Arzanol, an anti-inflammatory and anti-HIV-1 phloroglucinol α -pyrone from *Helichrysum italicum* ssp. *microphyllum*," *Journal of Natural Products*, vol. 70, no. 4, pp. 608–612, 2007.
- [16] J. Bauer, A. Koeberle, F. Dehm et al., "Arzanol, a prenylated heterodimeric phloroglucinyl pyrone, inhibits eicosanoid biosynthesis and exhibits anti-inflammatory efficacy *in vivo*," *Biochemical Pharmacology*, vol. 81, no. 2, pp. 259–268, 2011.
- [17] A. Rosa, M. Deiana, A. Atzeri et al., "Evaluation of the antioxidant and cytotoxic activity of arzanol, a prenylated α -pyrone-phloroglucinol etherodimer from *Helichrysum italicum* subsp. *microphyllum*," *Chemico-Biological Interactions*, vol. 165, no. 2, pp. 117–126, 2007.
- [18] A. Rosa, F. Pollastro, A. Atzeri et al., "Protective role of arzanol against lipid peroxidation in biological systems," *Chemistry and Physics of Lipids*, vol. 164, no. 1, pp. 24–32, 2011.
- [19] J. Vrkoč, L. Dolejš, P. Sedmera, S. Vašíčková, and F. Šorm, "The structure of arenol and homoarenol, α -pyrone derivatives from *Helichrysum arenaricum* (L.) moench," *Tetrahedron Letters*, vol. 12, no. 3, pp. 247–250, 1971.
- [20] A. Minassi, A. Giana, A. Ech-Chahad, and G. Appendino, "A regiodivergent synthesis of ring A C-prenylflavones," *Organic Letters*, vol. 10, no. 11, pp. 2267–2270, 2008.
- [21] A. Minassi, L. Cicione, A. Koeberle et al., "A multicomponent carba-Betti strategy to alkylidene heterodimers—total synthesis and structure—activity relationships of arzanol," *European Journal of Organic Chemistry*, no. 4, pp. 772–779, 2012.
- [22] A. Sala, M. del Carmen Recio, R. M. Giner, S. Máñez, and J. Ríos, "New acetophenone glucosides isolated from extracts of *Helichrysum italicum* with antiinflammatory activity," *Journal of Natural Products*, vol. 64, no. 10, pp. 1360–1362, 2001.
- [23] M. Dallaporta, E. Pecchi, S. Thirion, A. Jean, and J. Troadec, "Towards the management of inflammation: recent developments of mPGES-1 inhibitors," *Recent Patents on CNS Drug Discovery*, vol. 5, no. 1, pp. 70–80, 2010.
- [24] W. L. Smith, "The eicosanoids and their biochemical mechanisms of action," *Biochemical Journal*, vol. 259, no. 2, pp. 315–324, 1989.
- [25] A. Schneider, Y. Zhang, M. Zhang et al., "Membrane-associated PGE synthase-1 (mPGES-1) is coexpressed with both COX-1 and COX-2 in the kidney," *Kidney International*, vol. 65, no. 4, pp. 1205–1213, 2004.
- [26] D. P. Hajjar and K. B. Pomerantz, "Signal transduction in atherosclerosis: integration of cytokines and the eicosanoid network," *FASEB Journal*, vol. 6, no. 11, pp. 2933–2941, 1992.
- [27] J. B. Smith, H. Araki, and A. M. Lefer, "Thromboxane A₂, prostacyclin and aspirin: effects on vascular tone and platelet aggregation," *Circulation*, vol. 62, no. 6, pp. V-19–V-25, 1980.
- [28] J. Clàiria, "Cyclooxygenase-2 biology," *Current Pharmaceutical Design*, vol. 9, no. 27, pp. 2177–2190, 2003.
- [29] D. O. Stichtenoth, S. Thorén, H. Bian, M. Peters-Golden, P. Jakobsson, and L. J. Crofford, "Microsomal prostaglandin E synthase is regulated by proinflammatory cytokines and glucocorticoids in primary rheumatoid synovial cells," *Journal of Immunology*, vol. 167, no. 1, pp. 469–474, 2001.
- [30] M. Murakami, H. Naraba, T. Tanioka et al., "Regulation of prostaglandin E₂ biosynthesis by inducible membrane-associated prostaglandin E₂ synthase that acts in concert with cyclooxygenase-2," *The Journal of Biological Chemistry*, vol. 275, no. 42, pp. 32783–32792, 2000.
- [31] T. Kobayashi and S. Narumiya, "Function of prostanoid receptors: studies on knockout mice," *Prostaglandins and Other Lipid Mediators*, vol. 68–69, pp. 557–573, 2002.
- [32] C. D. Funk, "Prostaglandins and leukotrienes: advances in eicosanoid biology," *Science*, vol. 294, no. 5548, pp. 1871–1875, 2001.
- [33] M. Karin and Y. Ben-Neriah, "Phosphorylation meets ubiquitination: the control of NF- κ B activity," *Annual Review of Immunology*, vol. 18, pp. 621–663, 2000.
- [34] D. C. Douek, M. Roederer, and R. A. Koup, "Emerging concepts in the immunopathogenesis of AIDS," *Annual Review of Medicine*, vol. 60, pp. 471–484, 2009.
- [35] Z. Grossman, M. B. Feinberg, and W. E. Paul, "Multiple modes of cellular activation and virus transmission in HIV infection: a role for chronically and latently infected cells in sustaining viral

- replication," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 11, pp. 6314–6319, 1998.
- [36] A. M. Geretti, E. Hulskotte, and A. D. M. E. Osterhaus, "Cytotoxic T lymphocytes in AIDS pathogenesis: lessons to be learned from the macaque model of simian immunodeficiency virus infection," *Journal of General Virology*, vol. 79, no. 3, pp. 415–421, 1998.
- [37] V. Ayyavoo, A. Mahboubi, S. Mahalingam et al., "HIV-1 Vpr suppresses immune activation and apoptosis through regulation of nuclear factor κ B," *Nature Medicine*, vol. 3, no. 10, pp. 1117–1123, 1997.
- [38] T. D. Gilmore, "Introduction to NF- κ B: players, pathways, perspectives," *Oncogene*, vol. 25, no. 51, pp. 6680–6684, 2006.
- [39] S. K. Chauthe, S. B. Bharate, S. Sabde, D. Mitra, K. K. Bhutani, and I. P. Singh, "Biomimetic synthesis and anti-HIV activity of dimeric phloroglucinols," *Bioorganic and Medicinal Chemistry*, vol. 18, no. 5, pp. 2029–2036, 2010.
- [40] J. M. Lin, C. C. Lin, M. F. Chen, T. Ujii, and A. Takada, "Scavenging effects of *Mallotus repandus* on active oxygen species," *Journal of Ethnopharmacology*, vol. 46, no. 3, pp. 175–181, 1995.
- [41] B. Halliwell, "Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment," *Drugs and Aging*, vol. 18, no. 9, pp. 685–716, 2001.
- [42] A. C. U. Lourens, A. M. Viljoen, and F. R. van Heerden, "South African *Helichrysum* species: a review of the traditional uses, biological activity and phytochemistry," *Journal of Ethnopharmacology*, vol. 119, no. 3, pp. 630–652, 2008.



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