CORPUS PUBLISHERS

Advance Research in Sciences (ARS)

Volume 2, Issue 1, 2024

Article Information
Received date : 24 January, 2024
Published date: 08 February, 2024

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DOI: 10.54026/ARS/1015

Key Words
Coumarins; Immunomodulation; Immunosuppression; Autoimmune

Research Article

Coumarins and their Derivatives as Potential Modulators of Immune Response

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Abstract

Coumarins are molecules varying from simple to more complex compounds that are widely available in nature, while some of them have been synthesized. They possess significant pharmacological potential, but until now their applicability in medicine has been limited to their ability to limit coagulation in blood. Our immune system plays a major role in disease states, with both ends of the spectrum being significant. Both a slow or absent immune reaction on one hand and an overreaction of the system on the other hand may be detrimental to our health. Since the process of coagulation seems to be related to the immune system, studies showing a possible role for coumarins and their lead compounds in modulating the immune system. were searched for in databases like PubMed, Google Scholar and Hinari. Several studies with promising results revealing a role for coumarins in modulating the immune response, were found However, all these studies have been carried out in in vitro and simple animal models. Randomized clinical trials will be required to demonstrate the therapeutic value of these readily available coumarin compounds.

Introduction

The immune system plays a pivotal role in our bodily homeostasis. Generally, it is assumed that this system protects the human body from invading pathologic agents and chemicals by eliminating them [1,2]. However, in the past decades it became clear that the homeostatic effects of the immune system are beyond this traditionally accepted function [1,2]. For example, it functions as a sensor and way of communication with the central nervous system [2], it enhances cardiac function after ischemic damage [3], assists in maintaining the homeostasis in the intestines [4] and is even involved in the body metabolism [5]. It is thus not surprising that any dysfunction of the immune system may lead to disturbance of homeostasis and when sustained this may lead to disease conditions. Remarkably, both a deficient as well as an overactive immune system may lead to pathologic conditions. Examples of deficiency are immunodeficient conditions like AIDS [6] and in immunocompromised patients receiving chemotherapy for cancer [7]. Allergic [8], and rheumatic conditions [9] as well as autoimmune diseases [10] are examples of an overactive immune system. More recently COVID-19 emerged as a condition where a burst of immune reaction led to aggravation of the disease [11], possibly as a result of an imbalanced reaction of the cellular immunity [12].

The therapeutic management of these conditions includes induction of the immune system with vaccination [13], which achieved high attention again during COVID 19 [14], and bolstering of the system [15]. However, until now, the latter strategy did not result in successful pharmacologic or other agents. Recent advances resulted in the application of mono and polyclonal antibodies [16,17] that are administered preferably to modify rather than cure disease conditions like asthma [18] and diabetic retinopathy [19]. Management of overactive immune conditions is somewhat easier for example, corticosteroids [20] and chemotherapeutic agents. Notwithstanding this, their adverse effects [21,22] do not put them on the direct shortlist of everyday clinical practice. For these reasons, the search for newer, more effective and safer agents in the context of the immune system is continuing. Coumarin belongs to the 1,2-benzopyrone class of molecules and is abundant in many plants [23]. They are often found in the form of glycosides or esters. Coumaric compounds are lactones of 2–coumaric acid (2- hydroxy-Z- cinnamic acid). They fall into various classes like, simple coumarins, isocoumarins, furanocoumarins, pyranocoumarins (angular and linear), biscoumarins and phenylcoumarins [24] and their wide availability makes them the ideal lead compounds for research in pharmacology. For example, numerous studies showed that they possess meaningful anti-diabetic activity in *in silico*, *in vitro* and *in vivo* models [25]. Unfortunately, despite the wide availability of coumarins and their lead compounds and metabolites in natural products [26], their medical application until now has been mostly limited to the anticoagulant activity of warfarin derived from dicoumarol and its analogues [27]. Warfarin and its derivatives acenocoumarol and fenprocoumon are well-known for their thrombostatic properties [28]. In recent years, researchers described a possible link between the process of thrombosis and the immune system [29-31] For this reason, we aimed in this review to identify a possible role for coumarins in immune bolstering, immunomodulation or immunosuppression.

Methods

The PubMed, Google Scholar and HINARI databases were searched databases were searched for papers published about the effects of coumarin or its derivatives on the immune system. Only papers that were published in English or along with an English translation of at least the abstract after the year 2000, were included. The following search strings. “Coumarin and Immunity”, “Coumarin and immunoglobulins”, “Coumarin and inflammation”, “Coumarin and immunosuppression”. were entered in the search engines of these databases. Relevant papers were selected, and their reference list was also carefully searched for possible relevant papers.

Results

Table 1 provides an overview of the coumarin compounds and their probable effects.

Table 1: Overview of coumarins with immunomodulating effects.

Compound	Potential Activity	Reference
8-[(4-Chlorophenyl) sulfonyl]-7-Hydroxy-4-Methyl-2H-chromen-2-One	antimicrobial	[34]
pyrazole-coumarin hybrids	antimicrobial	[35]
4-bromopropoxycoumarin derivatives	Antimicrobial, cytostatic	[36]
coumarin-piperazine hybrids	Cytostatic	[37]
coumarin- N-heterocyclic hybrid	Antimicrobial	[38]
6-nitro-coumarin	Fungicide	[39]
7-(6-(2-methyl-imidazole))-coumarin	Antiviral	[40]
Coumarin	Antiviral	[41]
7-hydroxycoumarin	Enhanced immunity	[42]
6-methoxy-7-hydroxy- coumarin	Increased macrophage activity	[43]
7-methoxy-8-[3-methylpent-2-enyl] coumarin derivatives	Cytostatic	[44-48]
4-hydroxycoumarin	Antimetastatic	[49]
lepitodol	Immunosuppressive	[50]
6,6',7,7'-tetramethoxyl-8,8'-biscoumarin 7,7'-dihydroxy-6,6'-dimethoxy-8,8'-biscoumarin 7,7'-dimethoxy-6,6'-biscoumarin	Immunosuppressive	[51, 52]
2-[(8S)-2-oxo-8,9-dihydrofuro[2,3-h] chromen-8-yl] propan-2-yl (Z)-2-methylbut-2-enoate	Immunosuppressive	[53]
Urolithin A	Immunosuppressive	[54,55]
bibenzyl-phenylpropane coumarin hybrid	Immunosuppressive	[56]
6,7-Dihydroxy-2H-1-benzopyran-2-one	Anti-psoriasis, anti-colitis	[57, 63]
6-Methoxy-7-{[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxy}-2H-1-benzopyran-2-one	Anti-rheumatic	[58]
5,7-dihydroxy-6-(3-methylbutanoyl)-8-(3-methylbut-2-enyl)-4-phenylchromen-2-one	Immunosuppressive	[59]
6,7-dihydroxy-3-[3′,4′-methylenedioxyphenyl]-coumarin	Immunosuppressive	[60]
7,8-dihydroxychromen-2-one 3-(4-aminophenyl)-coumarin	Anti-rheumatic	[61,62]
4-arylcoumarin (5,7-dimethoxy-4-p-methoxyphenylcoumarin)	Anti-histaminic	[64]

Coumarins with potential immunity enhancing effects

One way to bolster the immunity of organisms is to present an abundancy of antigens to the immune system. This can be the result of destroying the causative microorganisms or cancerous cells [32,33]. In line with this, the 8-[(4-Chlorophenyl) sulfonyl]-7-Hydroxy-4-Methyl-2H-chromen-2-One coumarin derivative showed comparable antimicrobial activity against *M. tuberculosis* in Guinea pigs compared to the traditionally used drugs Isoniazid and Rifampicin [34]. In a similar way, pyrazole-coumarin hybrids inhibited the growth of the Mycobacterium-TB H37Rv strain [35]. Mycobacterium species are well known for their ability to stay under the radar of the immune system.

Furthermore, 4-bromopropoxycoumarin derivatives showed significant inhibiting effects in S. *aureus* species and the MCF-7 breast cancer mimicking cell line in *in silico* and *in vitro* models [36]. The latter was even better than the reference Doxorubicin. Trimethoxyphenyl-coumarin, coumarin-indole and coumarin-dihydroquinoxalone coumarin-piperazine hybrids effectively inhibited cancer growth in both *in vitro* and *in vivo* models probably through inhibition of polymerization of tubulin [37]. Several coumarin- N-heterocyclic hybrid compounds showed cytostatic and antibiotic activity in *in vitro* models [38]. Coumarins also show fungicidal activity, specifically the 6-nitro-coumarin and the prenylated coumarin osthenol showed significant fungicide activity against *Candida alba in vitro* [39].

In addition, the 7-(6-(2-methyl-imidazole))-coumarin reduced the viral titer of spring viremia of carp virus in zebrafish [40]. Feeding *Cherax quadricarinatus*, the Australian red claw crayfish, with low dose coumarin enhanced the cellular immunity of the animal and reduced the damage caused by white spot syndrome virus infection [41]. Addition of 7-hydroxycoumarin to the food of broiler chickens improved their health and growth in general and decreased their leucocyte cell counts significantly, which indicates that their state of immunity improved [42]. Scopoletin (6-methoxy-7-hydroxy- coumarin) increased the phagocytic ability of macrophages in a human based monocytic cell line [43]. Several 7-methoxy-8-[3-methylpent-2-enyl] coumarin (osthole) derivatives showed meaningful anti-tumor activity in cell culture models [42-48]. Moreover, the 4-hydroxycoumarin impairs the ability of melanoma cells to metastasize [49] and although this effect is probably not immune related, it may contribute to presenting tumorous antigens to the immune system.

Coumarins with potential immunosuppressive effects

In some conditions like rheumatic and autoimmune disease as well as allergic conditions, it is necessary to suppress rather than stimulate the immune system. Throughout history, coumarins have demonstrated to possess properties to suppress the immune system. The phenylcoumarin derivative lepitodol showed immunosuppressive activity possibly through inhibition of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 expression in cultures of endothelial cells [50]. Coumarins derived from Urtica dentata, including but not limited to 6,6',7,7'-tetramethoxyl-8,8'-biscoumarin, 7,7'-dihydroxy-6,6'-dimethoxy-8,8'-biscoumarin and 7,7'-dimethoxy-6,6'-biscoumarin suppressed the ability of cultured dendritic cells to stimulate effector T cell response [51] suppressed T-cell proliferation in an *in vitro* splenic model [52]. A similar effect was observed with 2-[(8S)-2-oxo-8,9-dihydrofuro[2,3-h] chromen-8-yl] propan-2-yl (Z)-2-methylbut-2-enoate [53]. The benzo-coumarin Urolithin A increased autophagy of macrophages [54]. Omphalocarpin (8-[(2S)-2-hydroxy-3-methoxy-2-methylbutyl]-5,7-dimethoxychromen-2-one) suppressed the inflammatory response in a mouse model of inflammation [55]. Investigators isolated a bibenzyl-phenylpropane hybrid with a coumarin core from *Dendrobium devonianum* and showed that it significantly suppressed T and B cells *in vitro* [56]

Esculetin (6,7-Dihydroxy-2H-1-benzopyran-2-one), a simple coumarin, improved the skin lesions and inflammatory parameters in a mouse model of psoriasis [57]. Another coumarin, scopoline (6-Methoxy-7-{[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxy}-2H-1-benzopyran-2-one), improved the lesions of an adjuvant-induced arthritis (AIA) in rats [58]. The bee derived 5,7-dihydroxy-6-(3-methylbutanoyl)-8-(3-methylbut-2-enyl)-4-phenylchromen-2-one effectively reduced the proliferation of Th-17 leucocytes *in vitro* and reduced the inflammatory response in an autoimmune mouse model [59]. In a rat model of rheumatoid arthritis, 6,7-dihydroxy-3-[3′,4′-methylenedioxyphenyl]-coumarin reduced the neutrophilic infiltration of the synovial fluids in the affected joints [60]. The simple coumarins 7,8-dihydroxychromen-2-one and 3-(4-aminophenyl)-coumarin showed significant improvement of collagen induced rheumatoid arthritis in rats [61,62]. Esculin, scoparone and daphnetin among other coumarins, reduced the inflammation in a rat model of colitis [63]. Finally, the 4-arylcoumarin (5,7-dimethoxy-4-p-methoxyphenylcoumarin) reduced the histamine level in a mouse model of allergy and suppressed secretion of interleukins from human mast cells [64].

Conclusion and Future Perspectives

The selected studies show that quite a number of coumarins or their derivatives possess the potential to influence our immune system. Several mechanisms are involved in this mechanism of action, but mostly along the inflammation pathways in

the organism [65]. In fact, they have been identified as being a very common structure in compounds possessing anti-inflammatory properties in zebrafish [66]. However, despite all these studies and their promising results, all of them have been carried out in *in vitro* and animal models. To make the next important step as meaningful agents in the treatment of disturbances in the immune system, randomized clinical trials to prove their applicability need to be conducted. For now, it seems a long way home.

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