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Research Article

COUMARIN (ESCULETIN) - AN ANTIRHEUMATOID ARTHRITIC COMPOUND: AN UPDATE

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ABSTRACT

Context: Esculetin is a natural polyphenolic compound. It is chemically 6,7-dihydroxycoumarin and one of the ingredients of *Cortex fraxini*, a Chinese traditional medicine. It is used as a dietary supplement and found as non-toxic. Recently, there are many research works evaluated on esculetin in arthritis with supported molecular mechanisms.

Objectives: Esculetin becoming more attractive prodrug for arthritis. Hence, the present minireview will consolidate the targeted site of esculetin in the treatment of arthritis over the past decade.

Results: The most important molecular mechanism of esculetin is an antioxidant activities with decreased level of reactive oxygen species/reactive nitrogen species. It also inhibited lipoxygenase 5, lipoxygenase 12, and tyrosinase enzymes. It reduces the inflammation by modulating the key inflammatory enzyme matrix metalloproteinase-1 activity. It also lowers the nitrous oxide and prostaglandin E2 level in synovial fluid. Esculetin derivatives such as 5-methoxy esculetin inhibited the activity of nitrogen-activated protein kinases. The updated data also reveal that esculetin suppresses the leukotriene B4 level in plasma of adjuvant-induced arthritis tested animals.

Conclusion: The presented update showed that esculetin may be useful as a tool in regulating the mechanism and physiological functions of the inflammatory mediators and enzyme. Hence, the presented review work may be considered as a scientific proof for the development of an attractive drug candidate for the patient with rheumatoid arthritis.

Keywords: Coumarin, Esculetin, Rheumatoid arthritis, Molecular mechanism.

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease. It influences around 1% of population. Around 80% of affected patients are disabled after 20 years. Economically accessible conventional medications are moderate acting and are having restricted adequacy and lead to many unwanted symptoms. Moreover, they do not enhance the long-term treatment of RA. Esculetin, 6,7-dihydroxycoumarin, is a coumarin subordinate found in different plants, *Cortex fraxini* is one of the generally utilized conventional Chinese prescriptions [1]. It has been shown that *Cortex fraxini* has different pharmacological impacts, including hostile to pathogenic [2], calming [3], analgesic [4], against malignant growth [5], antioxidative activity [6], neuroprotective [7], and vascular defensive impacts [8]. It is one of the fundamental dynamic elements of *Cortex fraxini*, has been used as expectorant, against tussive [9] cell reinforcement, hostile to bacterial, and hostile to tumor [10]. Particularly, esculetin, asculin, fraxin, and fraxetin are found in *Cortex fraxini* explored as major pharmaceutical active ingredients [11]. Esculetin is becoming more attractive prodrug for arthritis. Recently, there are many research works evaluated on esculetin in arthritis with supported molecular mechanisms. Hence, the present minireview will focused to consolidate the targeted site of esculetin in the treatment of arthritis over the past decade.

PROFILE OF THE COMPOUND ESCULETIN

Esculetin is aglycone of esculin, a coumarin glycoside naturally occurs in horse chestnut:

- *Aesculus hippocastanum.*
- *Aesculus california.*

Family: Sapindaceae

The term esculetin - derived from the genus name, *Aesculus.*

Properties of esculetin

- Molecular formula: $C_9H_6O_4$
- Molecular weight: 178.14 g/mole
- Physical state: Pale yellow amorphous powder
- Melting point: 265–270°C
- Solubility: Sparingly soluble in water. Readily soluble in methyl alcohol
- pH: Weakly acid.

Chemistry of esculetin

IUPAC name: 6,7-Dihydroxy-2H-chromen-2-one

6,7-dihydroxy-2-benzopyrone.

Chemical test

Ethanolic solution of the sample is treated with 0.5 ml of 10% ammonium hydroxide solution and examined under UV light. Intense fluorescence is observed esculetin form dark brown or black color complex with ferric salt.

Pharmacological properties

Anti-inflammatory effect

Esculetin decreases the production of NO to manage blood vessels and facilitates the organ tissue destruction swelling; then again, esculetin inhibits the production of soluble intercellular adhesion molecule (sICAM-1), which can decrease the adhesion reaction of leukocytes and endothelial cells in sequence to decrease inflammation [12]. Esculetin was found to secure myocardial from ischemia-reperfusion damage [13].

Table 1: A study report of esculetin on anti-inflammatory potential in arthritis

S. No.	Work done
1.	Studied effect the newly synthesized mitochondria-targeted esculetin for its antiatherosclerotic potential [23]
2.	Studied the cell - biotransformation glycoside derivatives (esculetin its 6-glycoside esculetin) using engineered *E. coli* and Neisseria polysaccharide amylosurase [24]
3.	Reported the antiadipogenic activity of esculetin. Through the modulation of antioxidant enzymes [25]
4.	Assessed pharmacological exercises and compound of esculetin and its derivatives [26]
5.	The results of their findings shown that the esculetin displayed stimulant-like impact which may be identified with the restraint of NF-KB pathway and the enactment of BNF/Trkb signaling [11]
6.	Revealed the potential effectiveness of esculetin in the treatment of mental issue with aggravation and oxidative pressure [27]
7.	Reported (for the 1st time) the 5-methoxy esculetin inhibited lipopolysaccharide instigated aggravation by smothering MAPK and AP-1 pathway in RAW 264.7 cells [28]
8.	Review work was done on compound, natural exercises, and medicinal properties of esculetin and its derivative [29]
9.	Investigated defensive impact esculetin in LPS make long aggravation might be credit halfway to the restraint of NF-KB and RhoA/Rho kinase pathway *in vivo* and *in vitro* [30]
10.	Studied and found out the inhibitory effect of esculetin on the coupling exercise of NF-KB and AP-1 in TNF-alpha treat vascular smooth muscle cells [31]
11.	Isolated coumarin and (herniarin esculetin, scopolin, and scopoletin) from *Santolina oblongifolia* and studied inhibitory action of eicosanoid release from ionophore-stimulated mouse peritoneal macrophages [32]
12.	Studied anti-inflammatory action of benzopyrones by inhibition of cyclo- and lipo-oxygenase using croton oil ear test in mice [33]
13.	Studied anti-inflammatory and peripheral analgesic activity of esculetin in animal model [34]
14.	Decrease the attachment response of leukocytes and additionally endothelial cells keeping in mind the end goal to decrease inflammation [35]
15.	Diminished the statement of framework MMP-1 (reduce inflammation) [12]
16.	Lowered the nitrous oxide (decrease tissue damage from inflammation) and PGE2 level in synovial liquid [36]
17.	Protected myocardial from ischemia-reperfusion by systemic inflammation [13]
18.	Studied antioxidant activities with decreased level of ROS/RNS (reduced DNA damage), inhibited the lipoxygenase and tyrosinase enzymes [37]

PGE2: Prostaglandin E2, MMP-1: Metalloproteinase-1, MAPK: Nitrogen-activated protein kinase, ROS/RNS: Reactive oxygen species/reactive nitrogen species, NF-KB: Nuclear factor-kappa B, AP-1: Activate or protein-1, BNF: Brain-derived neurotrophic factor, Trkb: Tropomyosin-related kinase receptor B, TNF: Tumor necrosis factor, *E. coli: Escherichia coli*

Antitumor effects

Esculetin is a phenolic composite that is found in regular plant items and produces apoptosis in various kinds of human malignant growth cells. Esculetin has been appeared to specifically produce tumor apoptosis in various types of malignant growths and is considered as a promising chemotherapeutic agent. Acute promyelocytic leukemia is a kind of disease, in which undevelopment cells called promyelocytes multiply uncommon. Esculetin is found to restrain the survival of human promyelocytic leukemia cells in a fixation ward and time-subordinate way [14,15].

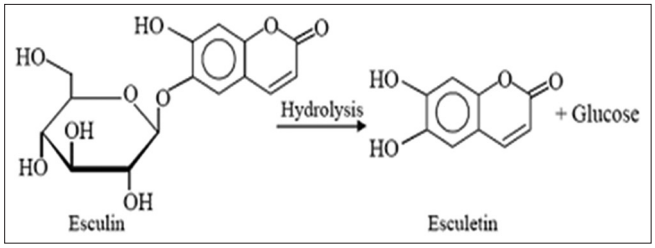


Fig. 1:

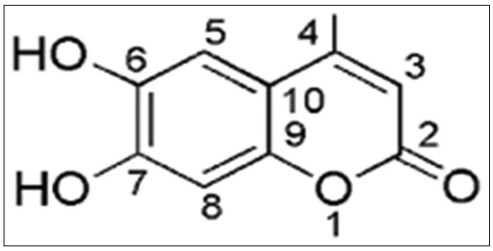


Fig. 2: Chemical structure of esculetin

Hepatoprotective effects

Esculetin is found to have against hepatotoxic movement and the manifestation of this compound in *Cichorium intybus* and *Bougainvillea spectabilis* may clarify the folkloric utilization of these plants in liver damage [16].

Antidiabetic effects

It was established on the research of Prabakaran, esculetin is the treatment and prevention of diabetes mellitus. It can reduce hyperglycemia-mediated oxidative stress by antioxidant competence in both hepatic and renal tissue [17].

Antibacterial effects

The human pathogen *Escherichia coli* are spread by direct or indirect contact with cause disease in animal and human stools. *E. coli* is the most widely recognized reason for hemorrhagic colitis. The expansion of esculetin to human fecal slurries and *in vitro* non-stop stream fermenter models reproducing conditions in the human colon and rumen caused checked reductions in the survival of a presented strain of *E. coli* [18].

Antioxidant effects

Esculetin is likewise an intense specialist in cells from reactive oxygen species (ROS)-mediated abeta destruction [19]. In another examination, esculetin is successful securing cells against DNA injury incited by oxidative pressure [16].

Inhibits of the proliferative of vascular smooth muscle cell (VSMC)

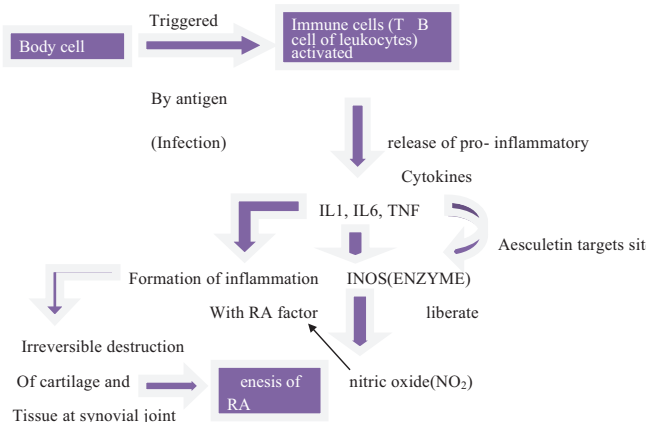
The multiplication of VSMCs incited by damage to the intima of supply routes is an essential pathogenic factor in vascular proliferative disarranges including atherosclerosis and restenosis. Esculetin can effectively interfere with the multiplication of rVSMCs *in vitro* in a portion and time-subordinate way [20].

Suppression of Adipogenesis

Esculetin has the impact of advancing glucose digestion and intervenes adipocyte apoptosis by the mitochondrial pathway starting the apoptotic procedure of 3T3-L1 adipocytes [21]. Another trial showed that esculetin has hostile to adipogenic impacts through adjustment of peroxisome proliferator-activated receptor γ and CCAAT/enhancer binding protein α by means of the AMP-activated protein kinase flagging pathway [22].

Flow diagram for pathogenesis of arthritis

- During sepsis - lipopolysaccharide (a bacterial endotoxin) released from bacteria trigger the macrophages for the production of tumor necrosis factor alpha (TNFα), subsequently interleukin (IL)-1 and IL-6.
- Both TNFα and IL can stimulate the production of collagenase and PGE 2 by synovial cells to cause joint damage in arthritis.
- In patient with RA, the synovial membrane is characterized by increased vascularity, infiltration of inflammatory cells, primarily CD4+T cells.
- The antigen-activated CD4+T cells stimulate monocytes/ macrophages to produce the cytokines IL-1, IL-6, and TNFα.
- These are the key cytokines and hallmark of inflammation in RA.



DISCUSSION

RA is a common autoimmune inflammatory disease. 80% of affected are disabled after 20 years. Rheumatoid joint pain is characterized by expanded vascular invade of fiery cells - CD4αT cells, which invigorate plasma cells to deliver proinflammatory cytokines IL-1, IL-6, and TNF. There are many research works around at the UN Food and Drug Administration approved drugs for RA the trend today, especially in all industrial settings are to seek the bioactive marker that will serve as compound for synthetic and semi-synthetic drug development to RA. In this concert, the present work an update was done on natural coumarin esculetin - a biomarker for the available scientific data in the management of inflammatory problem in RA. The most important molecular mechanism of esculetin is an antioxidant activity with decreased level of reactive oxygen species/ reactive nitrogen species (ROS/RNS). It also inhibited lipoxygenase 5, lipoxygenase 12, and tyrosinase enzymes. It reduces the inflammation by modulating the key inflammatory enzyme matrix metalloproteinase-1 activity. It also lowers the nitrous oxide and prostaglandin E2 level in synovial fluid. Esculetin derivatives such as 5-methoxy esculetin inhibited the activity of nitrogen-activated protein kinases. The updated data also reveal that esculetin suppresses the leukotriene B4 level in plasma of adjuvant-induced arthritis tested animals.

CONCLUSION

The presented review data revealed that the selected compound was investigated for different inflammatory activities in arthritis. Among the updated review of the biological effects and molecular mechanisms of esculetin, cell reinforcement action assumes an essential part connected with diminished levels of ROS/RNS, which is further conceivably identified with the counter proliferative, calming, against phospholipids disorder, and other pharmacological activities. The presented update showed that esculetin may be useful as a tool in regulating the mechanism and physiological functions of the inflammatory mediators and enzyme. Hence, the presented review work may be considered as a scientific proof for the development of an attractive drug candidate for the patient with RA.

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