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## Review article

# The endocannabinoid signaling pathway as an emerging target in pharmacotherapy, earmarking mitigation of destructive events in rheumatoid arthritis

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## ARTICLE INFO

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## ABSTRACT

Rheumatoid arthritis is an inflammatory autoimmune disease, characterized by synovial proliferation, destruction to articular cartilage and severe pain. The cannabinoids obtained from *Cannabis sativa* exhibited their actions via cannabinoid-1 and -2 receptors, which also provides a platform for endocannabinoids to act. The endocannabinoid system comprises endocannabinoid molecules involved in signaling processes, along with G-protein coupled receptors and enzymes associated with ligand biosynthesis, activation and degradation. The action of endocannabinoid system in immune system regulation, via primary CB2 activation, followed by inhibition of production of pro-inflammatory cytokines, auto-antibodies and MMPs, FLSs proliferation and T-cell mediated immune response, are elaborated as potential therapeutic regimes in rheumatoid arthritis. The involvement of endocannabinoid system in immune cells like, B cells, T cells and macrophages, as well as regulatory actions on sensory nociceptors to ameliorate pain is significantly highlighted in the review, elaborating the actions of endocannabinoid signaling in mitigating the disease events. The review also focuses on enhancement of endocannabinoid tone, either by inhibiting the degradation enzymes, like FAAH, MAGL, COX, CYP450, LOX, etc. or by retarding cellular uptake processes. Moreover, the review portrays the optimizing role of endocannabinoid system, in abbreviating the symptoms and complications of rheumatoid arthritis in patients and mitigating inflammation, pain and immune mediated effects significantly.

## 1. Introduction

Rheumatoid arthritis (RA) is a severe autoimmune disorder with a heterogeneous etiology, prevalent in 0.5–1% of the global population [1]. In countries like, USA and Europe, about 1% of the total population suffers from the disease [2]. The prevalence of this disease varies across the globe, with Nigeria with 0.1% prevalence rate (one of the lowest) to Pima and Chippewa with 5% prevalence rate (among the highest) [3]. Women and cigarette smokers are the most susceptible towards rheumatoid arthritis. Moreover, age is an important factor on which occurrence of this disorder depends. Rheumatoid arthritis is characterized by inflamed articular cartilage, gradual disability of the joints, and significant damage to the synovial joint and membrane [4]. However, rheumatoid arthritis, presently is associated with a diverse profile of

disorders like CV diseases, cancer risks, osteoporosis and psychological discrepancies [5]. The disease tends to disturb the quality of life and exhibits more likeliness to affect women more than men [6]. Therefore, the treatment portfolio of RA has always been a necessary paradigm. The immune system signaling molecules, mainly pro-inflammatory cytokines are involved in the progression of rheumatoid arthritis, like TNF and IL-6 [7]. RA therapies have not been introduced recently but in the 1990s bDMARDs were introduced targeting on specific agendas of RA pathophysiology achieving retardation in disease occurrence and clinical therapeutic goals [8]. TNF targeting biologic drugs, mainly etanercept, infliximumab, adalimumab, and certolizumab have been found to enhance improvement in patients and achieve 'treat to target' strategy in most of the patients [9]. However, about 30–40% of patients targeting TNF failed to achieve the desired clinical outcome or sustain

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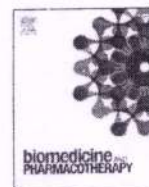
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Review

## Pleiotropic Effects of Polyphenols in Cardiovascular System

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## ARTICLE INFO

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Polyphenol  
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## ABSTRACT

Numerous epidemiological and clinical studies demonstrate the beneficial effects of naturally occurring, polyphenol supplementations, on cardiovascular system. The present review emphasizes on the risk factors associated with cardiovascular disorders (involving heart and blood vessels), and overview of preclinical and clinical trials on polyphenols for the treatment of cardiovascular diseases. The review collaborates PUBMED, Google Scholar and Research gate databases, which were explored using keywords and their combinations such as polyphenols, cardiovascular disease, flavonoids, atherosclerosis, cardiovascular risk factors and several others, to create an eclectic manuscript. The potency and efficacy of these polyphenols are mainly depending upon the amount of consumption and bioavailability. Recent data showed that polyphenols also exert beneficial actions on vascular system by blocking platelet aggregation and oxidation of low-density lipoprotein (LDL), ameliorating endothelial dysfunction, reducing blood pressure, improving antioxidant defenses and alleviating inflammatory responses. Several studies evidently support the cardioprotective actions mediated by polyphenols, however, some studies or long-term follow-up of human studies, did not demonstrate decisive outcomes because of variations in dose regimen and lack of appropriate controls. Therefore, more data is required to explore the therapeutic benefits of bioactive compounds as a preventive therapy for CVDs.

## 1. Introduction

Cardiovascular diseases (CVDs) or Heart diseases are prominent reasons of mortality across the globe. The World Health Organization (WHO) reports have depicted the annual deaths of about 17.9 million people, primarily due to CVDs including cerebrovascular and coronary heart disease (CHD). CVDs comprise of a numerous disorders related to

the heart and blood vessels, for example: peripheral arterial disease, stroke, atherosclerosis, hypertension, CHD, cerebrovascular disease and rheumatic cardiac disease. Among aforementioned CVDs, CHD is the major ground of the fatality, followed by stroke, which is the second prime cause of death [1]. The mortality rate associated with the progression of most of these diseases can be suppressed by mitigation of various risk parameters including, hypertension, obesity, tobacco and

**Abbreviations:** ACE, Angiotensin-converting enzyme; AGES, Advanced Glycation End Products; AHA, American Heart Association; APO, Apolipoprotein; BMI, Body Mass Index; BP, Blood Pressure; CHD, Coronary Heart Disease; cIMT, Carotid Artery Intima-media Thickness; CRP, C - reactive protein; CVDs, Cardiovascular Diseases; DM, Diabetes Mellitus; eNOS, Endothelial Nitric Oxide Synthase; FMD, Flow Mediated Dilatation; GLP-1, Glucagon Like Peptide-1; HDL-C, High Density Lipoprotein Cholesterol; LDL, Low Density Lipoproteins Cholesterol; IL, Interleukin; MDA, Malondialdehyde; MI, Myocardial Infarction; NT-proBNP, n-terminal Prohormone of Brain Natriuretic Peptide; oxLDL, Oxidized LDL; PWV, Pulse Wave Velocity; TC, Total Cholesterol; TG, Triglycerides; TNF, Tumor Necrosis Factor; TNF RI, Tumor Necrosis Factor Receptor I; TNF RII, Tumor Necrosis Factor Receptor II; VCAM-1, Vascular cell adhesion molecule-1; VLDL, Very Low Density Lipoproteins; WHO, World Health Organization.

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RESEARCH ARTICLE

**Evaluation of Anti-inflammatory and Anti-diabetic activities of  
*Actinodaphne madraspatana* bedd leaves**

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**ABSTRACT:**

The present study was carried out to find out the *in-vivo* anti-inflammatory and anti-diabetic activities of ethanol extract (200 and 400mg/kg) of leaves of *Actinodaphne madraspatana* (*A. madraspatana*) on Swiss Albino rats. The anti-inflammatory activity was investigated in carrageenan induced rat paw edema model which was compared with standard drug indomethacin at a dose level of 10mg/kg and the parameter measured being the paw volume by mercury displacements at 0, 15, 30, 60, and 120 minutes. The edema was induced in rats by administration of 1 % w/v solution of carrageenan in normal saline solution (1%w/v). The anti-diabetic activity was investigated in streptozotocin induced diabetic rat, which was compared with standard drug glibenclamide at a dose level of 4 mg/kg and the parameter measured being the blood glucose level on 0, 7, 14, 21 days. Diabetes was induced in rats by administration of streptozotocin (60mg/kg) in ice cold citrate buffer (pH 4.3). Results of pharmacological activities revealed that the ethanol extract of the plant leaves showed the significant ( $p < 0.001$ ) anti-inflammatory and anti-diabetic activities in a dose of 200mg/kg and 400 mg/kg body weight. The ethanol extract of leaves of *A. madraspatana* possess the anti-inflammatory and anti-diabetic activities.

**KEYWORDS:** *A. madraspatana* Leaves, Acute toxicity study, Ethanol extract, *In-vivo* pharmacological activities.

**INTRODUCTION:**

The use of medicinal plants and traditional medicines in developing countries as therapeutic agents for the maintenance of good health is well known in the literature. Medicinal plants containing various phytoconstituents are used to treat animal and human diseases and are considered as a rich resource of pharmacologically active ingredients which can be used in the development and synthesis of new drugs<sup>1</sup>.

Medicinal plants play a critical role in the development of human cultures and moreover, medicinal plants, considered as a source of nutrition, and are rich in fiber and antioxidants. Antioxidants compound possesses anti-atherosclerotic, anti-inflammatory, anti-bacterial, anti-viral, anti-carcinogenic, and anti-tumour activities to greater or lesser extent<sup>2</sup>. Medicinal plants have a promising future because there are about one million of plants around the world and most of their biological activities have not investigated yet and their biological activities could be decisive in the treatment of present or future studies<sup>3</sup>.

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To evaluate the impact of patient education on self-reported adherence, and management behavior of children with asthma

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### ABSTRACT

The failure to stick to a recommended remedial program for the treatment of an incessant illness might be mindful to some extent for proceeding with the infection movement. Adherence the key territories of enthusiasm for Asthma. The focal point of examination were to recognize issues detailed by families to influence their Adherence to asthma care. To evaluate the effect of patient education to Self-reported Adherence, Management, and Barriers. Children introducing during an intense assault of asthma were enrolled in this investigation. The restorative record of the experience were preoccupied and contrasted and data that were acquired at first visit and after 3 months. There are 986 youngsters 4 to 15 years old living in city evaluation tracts in the examination. The parental report of drugs endorsed, and the data on the disconnected report concurred 95.15% of the ideal opportunity  $\beta$ -Agonists, 86.24% are steroids, and 7.71% are cromolyn. Meds were overlooked a portion of time by 45.2% of the kids, and 52.8% attempted to escape to taking medication. Arrangements of follow-up consideration were kept by 69% of those given an arrangement, by an expected 60.0% of the individuals who were advised explicitly to require an arrangement. Just a single third of guardians report that they had the option to fend off the youngster from realized asthma triggers about constantly. After the subsequent, the huge changes are seen. Adherence to asthma-the executives program includes various territories: prescription, arrangement keeping, avoidance, and applying a crisis strategy. A barrier to Adherence may exist in one or every one of the four of these areas, prompting ineffectual control of asthma. The patient education improving the patient-doctor organization and furthermore improve Adherence.



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### INTRODUCTION

Asthma horribleness and mortality have expanded among kids who live inside a city environment. (Evans *et al.*, 1987) The particular reason this circumstance is obscure. To all the more likely comprehend and address this issue, The assignments of this exertion were two-fold: 1) figure out what variables were related with asthma dismalness in kids, and 2) build up an intercession address these variables. Non-Adherence to an endorsed remedial program were one of the indicated variables adding to asthma horribleness and mortality in all popula-



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