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PHARMACOLOGICAL PROPERTIES OF QUINALDIC ACID: A CONCISE REVIEW

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ABSTRACT

Quinaldic acid has been considered as an emerging therapeutic agent due to its diverse pharmacological and biochemical properties. Quinaldic acid is a quinoline derivative produced as a metabolite in the tryptophan kynurenine pathway. It is also produced by gut bacteria and present in Ephedra pachyclada plants as well. Quinaldic acid is a type of organic acid that shares structural similarities with quinoline derivatives. This review presents the pharmacological properties of quinaldic acid, encompassing its antiviral, antibacterial, anticancer, anti-inflammatory and antidiabetic effects. Experimental investigations revealed that quinaldic acid has shown concentration-dependent cytotoxic and antiproliferative actions on several cancer cell lines. Quinaldic acid reduced glucose production in the liver and increased insulin secretion, which helps to maintain glucose balance and manage diabetes. Additionally, quinaldic acid showed immunoregulatory effects in inflammatory diseases like rheumatoid arthritis. Furthermore, it has shown antibacterial efficacy against pathogenic gut microorganisms. Quinaldic acid thus may serve as a viable candidate for pharmaceutical development, with prospective uses in various therapeutic domains. Despite these wide-ranging biological effects, the exact mechanisms behind its various actions are not fully understood. This review highlights the pharmacological potential of quinaldic acid and emphasizes the need for further research to uncover its clinical applications.

KEYWORDS: Quinaldic acid, Cancer, Inflammation, Cytotoxicity, Diabetes mellitus.

INTRODUCTION

Heterocycles are organic compounds extensively found in nature and are essential to numerous biological processes.[1] Heterocyclic compounds are vital in metabolic reactions and necessary for cellular life.[2] The heterocyclic structure found in pyridines, pyrimidines, indoles, and quinolines substantially influences their pharmacokinetic and pharmacodynamic properties.[3] Quinolines are structural motifs present in various natural products.[4] Quinolines are bicyclic, nitrogen-containing heterocyclic chemical compounds that exist naturally and are significant constituents in both synthetic molecules and pharmacologically active agents.[5] Due to its extensive range of biological activities and well-known therapeutic potential, quinoline derivatives have evolved into one of the most promising groups of chemical substances.[6] Among the several quinoline derivatives, quinaldic acid is regarded as appealing especially due to their substantial promise for various biological and pharmacological uses.[7]

Quinaldic acid [QA] commonly referred to as quinoline-2-carboxylic acid, is an organic chemical compound.[8,9] It is a quinoline derivative in which the hydrogen atom at the second position of the quinoline ring is substituted by a carboxyl (–COOH) group[9] (Figure 1). This structural alteration imparts unique chemical characteristics to QA and rendering it as an invaluable intermediary in the synthesis of several physiologically active and therapeutic substances.[10] QA is primarily produced as a metabolite of tryptophan in several living organisms.[11] QA (quinoline-2-carboxylic acid) is structurally comparable to pyridine carboxylic acids, although features a more extensive conjugated aromatic structure.[12] It has been frequently used as a ligand in organometallic chemistry[7] and as a vital synthetic intermediate in medicinal research.[13] Moreover, QA and

its derivatives offer promising avenues for the synthesis of bioactive molecules and show a diverse array of therapeutic capabilities, encompassing anticancer, antiviral, estrogenic, antidiabetic, antibacterial, cytotoxic, and antiproliferative properties.[14,15,16,17,18,19,20]

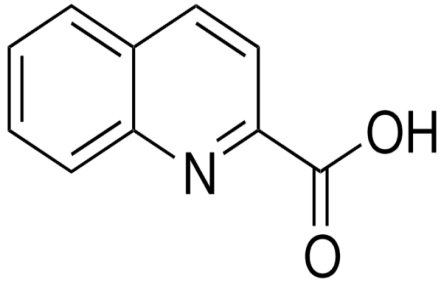

Figure 1: Structure of Quinaldic acid.

Natural Sources of QA

Ephedra pachyclada is a non-flowering seeded plant within the Ephedraceae family, with extensive geographical distribution.[21] As of now, approximately 60 species of Ephedra have been discovered, encompassing more than 100 compounds, including alkaloids, flavonoids, tannins, sugars, and phenolic acids. This herb has traditionally been employed to treat numerous maladies, such as asthma, liver disorders, skin diseases, fever, nasal congestion and bronchitis and inflammation. QA has been specifically isolated from natural sources, which is found in the stems of the plant Ephedra pachyclada.[18]

Search Strategy

A literature investigation on the medicinal potential of QA was performed utilizing prominent indexing databases, such as PubMed, Scopus, ScienceDirect, Web of Science and Google Scholar. Relevant studies were located utilizing keywords including "QA," kynurenine derivative, tryptophan metabolite and carboxylic acid. Only peer-reviewed articles and review papers demonstrating well defined mechanisms and solid experimental procedures were included. This study seeks to deliver a thorough examination of the therapeutic importance of QA and to highlight promising avenues for further investigation.

Biological Activities of QA

The active substance QA has been documented to exhibit a broad spectrum of pharmacological properties, including antiproliferative, antidiabetic, cytotoxic, anti-inflammatory, antibacterial, and antiviral effects. These effects likely arise from its ability to interact with key enzymes, metabolic pathways, and cellular signaling networks. The following sections summarize the current experimental findings on its pharmacodynamic profile.

Antiviral Activity of QA

Several compounds exhibited significant antiviral effectiveness at low concentrations with minimal cytotoxicity, suggesting an optimistic therapeutic index. Their supplementary virucidal characteristics and capacity to surmount medication resistance further emphasize their medicinal importance. QA serves as an intriguing framework in medicinal chemistry, facilitating the discovery of innovative antiviral compounds with enhanced efficacy and safety profiles.

Shibnev et al.[22] reported that the new amino acid derivatives containing carbocyclic frameworks of adamantane and QA have been synthesized and investigated for their in vitro antiviral efficacy against the Influenza A/H5N1 virus. Experimental investigations utilizing cultivated embryonic porcine kidney epithelial (SPEV) cells revealed that these substances proficiently impede virus propagation. QA derivatives, namely quinaldyl-L-serine methyl ester (QS) and quinaldyl-L-tryptophan methyl ester (QT), were evaluated for their cytotoxic and antiviral activities. The results indicated that these compounds demonstrate modest antiviral efficacy, especially when given late infection, with inhibitory concentration (ID_{50}) values < 0.06 mg/ml, signifying their ability to impede viral proliferation under specific circumstances. The antiviral effectiveness of these compounds has been shown to be concentration-dependent, exhibiting quite constrained therapeutic window, particularly in preventive applications. Cytotoxicity studies revealed that QS exhibited reduced toxicity ($CT_{50} \geq 1.0$ mg/ml), while QT shown relatively greater toxicity, indicating that the characteristics of the amino acid moiety substantially impact biological activity.

Antibacterial Activity of QA

QA exhibited selective action, specifically targeting pathogenic bacteria while preserving the integrity of normal gut flora. Lee et al.[23] regarded this as a significant advantage due to the fact that several conventional antibiotics also eliminate beneficial bacteria. The antibacterial efficacy of methanolic extracts of QA prepared from the stems of Ephedra pachyclada was comprehensively examined against intestinal bacteria utilizing the paper disc agar diffusion technique. The methanolic extract exhibited significant inhibitory efficacy against Clostridium perfringens, while exerting negligible or no impact on beneficial bacteria including Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus casei, and Escherichia coli. Subsequent fractionation of QA indicated that the chloroform fraction had the maximum antibacterial potency, resulting in the effective extraction of the active component via silica gel chromatography and HPLC. Thorough spectroscopic investigations, encompassing UV, EI-MS, ^{1}H-NMR, and ^{13}C-NMR, validated the compound's identity as QA, a derivative of quinoline. QA exhibited substantial, dose-dependent antibacterial efficacy especially against pathogenic gut bacteria. It had potent inhibitory effects at 1.0 mg/disc and moderate effectiveness at reduced dosages (0.5 and 0.1 mg/disc) against Clostridium difficile and Clostridium perfringens. QA mechanistically disrupt bacterial DNA binding and

hinder replication and transcription processes, hence enhancing their antibacterial activity. QA is a noteworthy natural antimicrobial candidate characterized by selective efficacy and an enhanced safety profile, rendering it a significant lead molecule for potential drug development.

Cytotoxic Activity of QA

Quinone and quinone-derived compounds have received considerable interest owing to their extensive biological activity, especially their anticancer and anti-inflammatory effects. Imraish et al.[20] explored the cytotoxic effects of QA on the A549 human lung cancer cell line utilizing the MTT assay. The results demonstrated a distinct concentration-dependent progression in cytotoxicity, with QA showing increased toxicity at elevated concentrations relative to PEG. In addition, QA elicited dose-dependent cytotoxicity in A549 lung cancer cells chiefly via producing reactive oxygen species (ROS), which impaired mitochondrial function and decrease cellular metabolic activity. Despite its cytotoxic properties, QA may also demonstrate anti-inflammatory and anticancer properties by obstructing critical signaling pathways such as NF-κB, hence mitigating inflammation-induced tumor development.

Anti-inflammatory Activity of QA

Nowicka et al.[24] demonstrates QA substantial biological action, particularly in modulating synoviocyte behavior, which is pivotal in the advancement of rheumatoid arthritis (RA). QA serves as an endogenous regulator by suppressing synoviocyte proliferation and motility in a dose-dependent manner, therefore regulating aberrant cell growth in joint tissues. Mechanistically, this action is facilitated by the modulation of critical signaling pathways (ERK, p38 MAPK, PI3K/Akt) and is amplified by kynurenic acid, playing a role in the regulation of inflammation and joint homeostasis in rheumatoid arthritis. Moreover, its capacity to function as a metal ion chelator may enhance its protective action in inflammatory diseases associated with metal imbalance. These findings indicate that QA serves as an intrinsic regulator of synoviocyte survival and joint homeostasis and its diminished levels in rheumatoid arthritis may lead to excessive fibroblast proliferation and joint injury. Consequently, QA is an intriguing option for further exploration as a possible therapeutic target in inflammatory and proliferative joint illnesses.

Antidiabetic Activity of QA

Inhibitory activity against α-amylase and α-glucosidase

QA or quinoline-2-carboxylic acid, has emerged as a potentially bioactive drug with substantial therapeutic potential, especially in metabolic illnesses like diabetes mellitus. The bioactive ingredient in the chloroform fraction of Ephedra pachyclada stems was efficiently extracted by silica gel column chromatography and subsequent preparative HPLC. The molecule was characterized as quinoline-2-carboxylic acid. The antidiabetic efficacy of quinoline-2-carboxylic acid and its structural variants was assessed through its inhibitory activity against α-amylase and α-glucosidase, with acarbose serving as the standard reference. Of the substances evaluated, quinoline-2-carboxylic acid demonstrated the highest inhibitory efficacy, with IC_{50} values of 15.5±1.9 µg/mL for α-amylase and 9.1±2.3 µg/mL for α-glucosidase, surpassing both its derivatives and acarbose. These findings illustrate the pivotal significance of the carboxyl functional group in augmenting enzyme inhibition. The findings indicate that quinoline-2-carboxylic acid and its derivatives exhibited considerable antidiabetic potential by efficiently regulating essential enzymes in glucose metabolism, implying its role as novel therapeutic agent.[25]

Inhibition of hepatic gluconeogenesis

Hanson et al.[26] reported that QA has a strong hypoglycemic effect by inhibiting liver gluconeogenesis. In experiments using isolated rat liver preparations, QA significantly reduced glucose production from key gluconeogenic sources like lactate, pyruvate, and alanine. The compound was found to affect phosphoenolpyruvate carboxykinase (PEPCK), which is the rate-limiting enzyme that converts oxaloacetate to phosphoenolpyruvate. This process is a crucial step in glucose production. Notably, QA did not change glycolytic activity, confirming that it specifically blocks gluconeogenic pathways while leaving normal carbohydrate metabolism intact. In vivo studies supported these findings, revealing a significant drop in blood glucose levels in the treated animals. These results suggest that QA could be a specific inhibitor of liver glucose production, pointing to its potential use in treating metabolic disorders, including type 2 diabetes mellitus.

Modulation of insulin secretion and biosynthesis

Beyond liver metabolism, QA also affects pancreatic β-cell function. Okamoto et al.[27] studied the impact of QA and its hydroxy form, 8-hydroxyquinaldic acid (8-HQA), on insulin release in isolated rat Langerhans islets. Both substances significantly boosted insulin release, more than other kynurenine metabolites like kynurenic acid and xanthurenic acid. Okamoto et al.[28] showed that QA and 8-HQA significantly reduced proinsulin production in isolated rat islets without affecting the conversion of proinsulin to insulin. This specific suppression indicates that QA plays a regulatory role in insulin production, likely serving as a physiological feedback modulator within β-cells. Together, these studies suggest that QA has a dual role in pancreatic function. It stimulates insulin release while limiting excessive proinsulin production, helping to maintain β-cell balance and energy regulation.

Antiproliferative Activity of QA

QA showed promising anticancer potential, particularly against colon cancer cells. It exhibited a concentration-dependent reduction in metabolic activity in colon cancer cell lines HT-29, LS-180, and Caco-2, with IC_{50} values

of 0.5 mM, 0.5 mM and 0.9 mM. Furthermore, QA exhibited no toxicity to normal colon epithelial cells (CCD841CoTr). QA exhibited substantial anticancer efficacy by reducing DNA synthesis and obstructing critical signaling pathways, including ERK1/2 and p38 MAPK, thus decreasing metabolic activity and successfully restraining colon cancer cell proliferation without inducing damage. These pathways are essential regulators of cellular proliferation, differentiation, and gene expression and their dysregulation is frequently linked to cancer progression. Moreover, its modulation of the PI3K/Akt pathway highlights its potential as a targeted drug for regulating cancer proliferation and improving therapeutic efficacy.[19]

Langner et al.[29] showed that QA was found to activate the tumor suppressor p53 pathway in LS180 colon cancer cells. Treatment with QA significantly raised both p53 gene and protein levels in a way that depended on dosage and time. Immunofluorescence confirmed that p53 moved into the nucleus and cytoplasm more after QA treatment. Despite clear cell cycle arrest, no apoptosis or cell death was noted, which means QA mainly slows growth through p53/p21 without directly killing cells. QA exhibited anticancer properties by elevating the expression of the tumor suppressor p53 at both transcriptional and protein levels, consequently optimizing cell cycle regulation in colon cancer cells. By triggering p53-dependent pathways, it effectively suppresses cell proliferation. Overall, these findings position QA as a promising chemopreventive and anticancer agent that specifically targets cancer cell growth while protecting normal tissues. QA displayed potent anti-inflammatory and anticancer activity by attenuating inflammation in macrophages without inducing cytotoxicity and efficiently decreasing the proliferation of cancer cells. Its ability to chelate metal ions via the interaction of its carboxyl group and nitrogen atom enhances its potential as a viable repurposed pharmaceutical agent.[30]

CONCLUSION

QA is a multifunctional molecule derived from quinoline, exhibiting a wide range of pharmacological properties, hence presenting it as a potential competitor in contemporary drug research. It showed anticancer, anti-inflammatory, antibacterial, antiviral and antidiabetic properties highlighted its medicinal promise. Its capacity to selectively target neoplastic cells, modulate critical biological signaling pathways and suppress harmful microbes while preserving normal flora has considerable advantages compared to conventional therapies. Moreover, its function as a natural metabolite and its participation in biological pathways augment its significance in both physiological and clinical conditions. The dual character of its biological activity, especially its interaction with various signaling pathways, necessitates more mechanistic investigations and in vivo assessments. Subsequent investigations concentrating on structural alterations, pharmacokinetics and clinical validation will be essential to fully exploit the therapeutic potential of QA and transform it into useful clinical applications.

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