Review of the chemistry and pharmacology of 7-Methyljugulone

Armelle T. Mbaveng*, Victor Kuete

Department of Biochemistry, Faculty of science, University of Dschang, Cameroon.

Abstract
Background: Naphthoquinone is a class of phenolic compounds derived from naphthalene. 7-Methyljugulone (7-MJ) is a naphthoquinone also known as ramentaceone or 6-Methyl-8-hydroxy-1,4-naphthoquinone or 5-Hydroxy-7-methyl-1,4-naphthoquinone or 7-Methyl-5-hydroxy-1,4-naphthoquinone or 5-Hydroxy-7-methyl-1,4-naphtoquinone or 7-Methyl-5-hydroxynaphthalene-1,4-dione. This compound is a biologically active naphthoquinone, with a molecular weight of 188 g/mol mostly isolated in the genus Diospyros and Euclea.

Objectives: This review was aimed at providing available chemically and pharmacological data on 7-MJ.

Methods: The chemical and pharmacological data were retrieved from the well-known scientific websites such as Pubmed, Google Scholar, Reaxys, Scirus, Scopus, Sciencedirect, Web-of-knowledge and SciFinder.

Results: 7-MJ was reported to have a variety of pharmacological activities such as antibacterial, antifungal, anticancer, antitubercular, anti-inflammatory and antiviral activities. The hemi-synthesis of the compound have been described.

Conclusions: The present review pooled out together the knowledge on 7-MJ, and can serve as the start point for future research and valorization accomplishments.

Key words: 7-methyljugulone; biosynthesis; in vitro synthesis; pharmacology

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Introduction
Naphthoquinone is a class of phenolic compounds derived from naphthalene occurring to some extent in fungi and are extremely common in higher plants and contain the naphthalene nucleus with two carbonyl groups on one nucleus usually at the ortho or para position (bicyclic). Naphthoquinones are widely distributed in plants, fungi and some animals and many were found to exhibit interesting range of pharmacological properties such as antibacterial, antifungal, anticancer, antimalarial and antiviral activities. Other quinone-related scaffolds such as 2-H-pyran-3(6H)-one derivatives and 2,3-dideoxyhexenopyranosides are also known for their biological activities against Staphylococcus species and Mycobacterium tuberculosis. Interestingly, 7-MJ, a naphthoquinone exhibits most of these activities. Therefore, we undertook the present review to bring out pharmacological knowledge on 7-MJ. We also discussed herein the biosynthesis and the in vitro synthesis of this compound.

Correspondence author:
Armelle T. Mbaveng
Department of Biochemistry, Faculty of science, University of Dschang, Cameroon
P.O. Box 67 Dschang-Cameroon
Email: armkuete@yahoo.fr
Biosynthesis and in vitro synthesis

It has been shown that higher plants have developed at least three separate pathways for the synthesis of the naphthoquinone carbon skeleton, including the shikimate, the homogentisate and the polyacetatemalonate pathways. The two main ways of naphthoquinones biosynthesis in higher plants include direct incorporation of shikimate or the homogentisic acid pathway involving the condensation of mevalonic acid and most probably toluhydroquinone. It was demonstrated that 2-Methyl-juglone (plumbagin) by its striking structural similarity with juglone and menadion was expected to be formed via the shikimate pathway, by C-methylation of Juglone in the 2 position.

According to Durand and Zenk plumbagin and 7-MJ are the first naphthoquinones in higher plants shown to be formed according to the acetate pathway which has long been known for the formation of naphthoquinones in fungi. An hexacetyl chain leads to the formation of these naphthalenes.

The synthesis of 7-MJ was realized by Mahapatra as follows: A mixture of anhydrous AlCl₃ (40 g, 300 mmol) and NaCl (8 g, 137 mmol) were heated to 180°C. A mixture of appropriate 4-halo-3-methyl phenol (10.7 mmol) or 4-halo-2-methyl phenol and maleicanhydride (4 g, 40.8 mmol) was added to the above melt with vigorous stirring for 2 min, and then poured into a mixture of ice and 12 M HCl. The mixture was kept for 30 min, and the precipitate was filtered and dried at room temperature overnight. The residue obtained was powdered and extracted with n-hexane with vigorous stirring at 50°C. The extract was concentrated under reduced pressure and crystallized from chloroform to afford the halogenated products 2-5.

A solution of 3 (200 mg, 0.90 mmol) in THF (20 mL) was added dropwise to a solution of SnCl₂ (1.0 g, 51 mmol) in 4 M HCl/THF (20 mL) at 60°C and stirred for 3 h. It was then cooled and filtered into a solution of FeCl₃. The resulting precipitate was filtered and dried to afford 7-MJ (Fig. 2).

The antifungal activities of 7-MJ were reported against Cryptococcus neoformans [50% inhibition of growth concentration (GI₅₀) of 0.3 µg/mL and a Minimal Inhibitory Concentration (MIC) of 1 µg/mL], Candida albicans (GI₅₀: 0.3 µg/mL; MIC: 20 µg/mL), Saccharomyces cerevisiae (GI₅₀: 0.3 µg/mL; MIC: 1 µg/mL) and Aspergillus niger (GI₅₀: 5 µg/mL; MIC: 300 µg/mL). 7-MJ also displayed antifungal activities against Phomopsis obscurans [inhibition percentage (IP) of 97%] and Phomopsis viticola (IP of 53.4 - 54.3%) at 202
7-MJ also demonstrated inhibitory activities against the Gram-positive oral streptococci, Streptococcus mutans (MIC of 156 μg/mL) and S. sanguis (MIC: 78 μg/mL) as well as against the Gram-negative anaerobic rods Prevotella gingivalis (MIC: 39 μg/mL) and P. intermedia (MIC: 78 μg/mL) frequently associated with human periodontitis known as gum disease. The antibacterial activity of this compound was also reported against M. luteus (GI_{50}: 20 μg/mL; MIC: 1000 μg/mL). 

7-MJ showed an exceptional antitubercular inhibitory effects against Mycobacterium tuberculosis H37Rv with a MIC value of 0.5 μg/mL combined to a very good selectivity index of 30.22 on normal vero cells. This compound was found to react as potent subversive substrate for the NADPH-dependent enzyme mycothiol disulfide reductase of M. tuberculosis, which is one of several potential biological targets for it anti-mycobacterial activity. In fact, M. tuberculosis lacks glutathione, instead it maintains millimolar concentrations of the structurally distinct low molecular weight thiol mycothiol (MSH). Analogous to glutathione, MSH plays an important role in oxidative stress management and is oxidized to the symmetrical disulfide (MSSM) in the process. The NADPH-dependent enzyme mycothiol disulfide reductase (Mtr) helps to maintain an intracellular reducing environment by reducing MSSM back to MSH. MSH is essential for the growth of M. tuberculosis and MSH-deficient mycobacteria exhibit increased sensitivity to oxidative stress making this redox pathway a potential biological target for novel antitubercular chemotherapies. 7-MJ also showed a very good antimycobacterial activity on other mycobacteria, with MIC values as low as 1.55 μg/mL against M. bovis, 1.57 μg/mL against M. smegmatis and 1.55 μg/mL on M. fortuitum. A 50% inhibition of growth concentration was also reported to be 5 μg/mL against M. avium.

7-MJ displayed antiviral activities through the inhibition of recombinant reverse transcriptase of HIV-1 with 80 to 100% inhibition at the concentration ranges of 12.5 to 100 μg/mL. This phytochemical also inhibited the human rhinovirus 3C protease with an IC_{50} value of 6.4 μM.

The cytotoxicity of 7-MJ was reported on several cancer cell lines including human oral epidermoid carcinoma [KB (IC_{50} value of 4.1 μM)], the human lung cancer cells [Lu1 (IC_{50}: 13.2 μM)] and hormone-dependent human prostate cancer cells [LNCaP] (IC_{50}: 3.7 μM). Though this compound was less toxic against the normal monkey kidney vero cells, its toxicity toward the Umbilical Vein Endothelial Cells (HUVEC) was rather found to be higher (IC_{50}: 5.7 μM) clearly indicating that possible chemotherapy involving pregnant women should be taken with caution. At 10 μM, 7-MJ induced apoptosis against leukemia HL60 cells with the percentage of Sub-G1 phase ranged from 10.3 - 27.5% whilst the IC_{50} value of 8.75 μM was reported on this cell line.

Discussion

7-MJ was isolated mostly in the family Moraceae, especially in the genus Diospyros and Euclea. The occurrence of naphthoquinones in the two genera has been documented. Its partial synthesis has also been described, suggesting that the compounds can easily be available for any in vivo and possible clinical studies. Phytochemicals are routinely classified as antimicrobials on the basis of susceptibility tests that produce MIC in the range of 100 to 1000 mg/mL. Activity is considered to be significant if MIC values are below 10 μg/mL for pure compound, moderate when 10<MIC<100 μg/mL and low when the MIC values is above 100 μg/mL. On this basis, 7-MJ can be considered as significantly effective antimicrobial compound against Saccharomyces cerevisiae (MIC: 1 μg/mL) and M. smegmatis (1.57 μg/mL) and M. fortuitum (1.55 μg/mL). This clearly shows that this compounds can be explored more as potential drug against some pathogenic fungi and bacteria. In the US NCI screening program, a compound is generally considered to have in vitro cytotoxic activity, if the IC_{50} value following incubation between 48 and 72 h, is less than 4 μg/mL or 10 μM.

On this basis, 7-MJ can also be considered as a good cytotoxic compound against several cancer cell lines such as KB, Lu1 and LNCaP. Its selectivity toward cancer cells as compared with the normal vero monkey kidney cells suggests that this compound is relatively safe for a potential anticancer treatment. Nevertheless, its toxicity toward the HUVEC indicated that caution should be taken when a potential treatment involve a pregnant women.

Conclusion

The present review obviously showed that 7-MJ could...
move forward into in vivo studies, in regards to its enormous pharmacological activities. Also, the study of the possible drug-drug interaction of 7-MJ is to be investigated. However, 7-MJ displayed high toxicity in HUVEC cells, clearly indicating that caution should be taken for any treatment involving pregnant women. The easy way of the in vitro chemical synthesis of 7-MJ ensure the availability of the compound for necessary future studies. Finally, the present work can served as a the future starting point for the developments of pharmaceutical from this potentially potent biological molecule.

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