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Comparative study of antioxidant and antimicrobial activity of berberine-derived Schiff bases, nitro-berberine and amino-berberine

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ABSTRACT

In recent years, the scientific community has focused on traditional natural products and their potential therapeutic benefits. Berberine is a plant-derived isoquinoline alkaloid with a variety of biological properties and identified as a promising pharmacophore for discovering new therapeutic agents against various diseases. However, unfavorable pharmacokinetic properties of berberine have limited its clinical application so much that researchers pursue its structure modification to overcome this problem. This study focuses on the synthesis of new berberine derivatives to improve its antioxidant and antimicrobial potentials, which were characterized using CHNO and NMR instruments. Berberine extracted from barberry root was nitrated, reduced to amine and condensed with benzaldehyde derivatives to produce berberine-based Schiff bases. The H atom donating ability of all compounds was measured against DPPH free radicals, with IC_{50} values ranging from 18.28 to 108.20 μg ml^{-1}. All berberine-based Schiff bases exhibited stronger antioxidant activity than nitro-berberine and amino-berberine. Only Schiff base derived from 4-hydroxybenzaldehyde showed slightly better antioxidant effects than original berberine. The inhibitory effects of the synthesized compounds were evaluated against important pathogenic fungal and bacterial strains using disk diffusion assays, with inhibition zone diameters ranging from 8.36 to 25.48 μg ml^{-1}. Berberine itself only affected *Candida albicans* fungus. Nitrated berberine was effective against all microorganisms except Gram-negative *Acinetobacter baumannii*. The results suggest that structural modifications and functionalization can enhance the antimicrobial and antioxidant properties of berberine.

1. Introduction

Isoquinoline alkaloids are the second-largest group of herbal alkaloids with a wide range of biological properties including anti-tumor, anti-microbial, anti-inflammatory, narcotic, anti-tussive, anti-oxidant and analgesic [1–5]. Berberine, a naturally occurring isoquinoline-based quaternary alkaloid, is one of the most important alkaloids found in barberry root bark, which is also known as

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Coptis rhizome. It is a yellow solid nearly insoluble in water with a bitter taste [6,7]. Recent studies showed that berberine had antioxidant [8], anti-tumor [9], anti-inflammatory [10], anti-fungal [11], anti-mutagenic [12], anti-diabetic [13], blood sugar-lowering [14], cholesterol-lowering [15], neuroprotective and liver-protecting effects [16]. The intestine and liver both play crucial roles in the metabolism of berberine. In liver cells, it is metabolized with the assistance of cytochromes and UDP glucuronosyltransferases.

The treatment of infectious diseases caused by drug-resistant fungal and bacterial strains is becoming increasingly challenging [17–19]. Synthesizing new antimicrobial agents is one way to combat these strains [20,21]. Schiff bases are a significant family of organic compounds that have made substantial contributions to the advancement of science, particularly in medicinal chemistry [22,23]. They are promising target molecules due to their various pharmacological and biological properties, including but not limited to analgesic, antiviral, antimalarial, anti-inflammatory and antiproliferative [24–26]. Among them, antimicrobial activities have received significant attention. Typically, they inhibit the growth of target microorganisms by intercalating and/or cleaving their DNA. Recent studies have shown that conjugating Schiff bases with chitosan, amino acids or nanoparticles can enhance their antimicrobial effects [27]. Schiff bases feature a C═N bond or imine group and are usually synthesized *via* condensation of primary amine with carbonyl compounds (Scheme 1) [28–31]. These compounds were first discovered and named in 1846 by the Italian chemist Hugo Joseph Schiff [32–34].

The biological properties of berberine can be improved through structural changes and functionalization [35,36]. Researchers have focused on designing and synthesizing new berberine derivatives with enhanced biological activities through modifications at positions especially C8, C9, C10, C12 and C13 [37,38]. Fig. 1 illustrates the different functionalization sites of berberine. Modifications at the C12 position, in particular, have been shown to increase its antimicrobial, antiviral, and anticancer properties [39].

Traditional and modern medicinal applications of berberine derivatives have encouraged us to synthesize new berberine-based Schiff bases [40,41]. In this purpose, berberine was extracted from barberry root, substituted at the C12 position, condensed with nine benzaldehyde derivatives to generate new Schiff bases. Finally, the inhibitory effect of the synthesized derivatives was investigated against DPPH (2,2-diphenyl-1-picrylhydrazyl) free radicals and human pathogenic microbes including *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus fumigatus*, *Staphylococcus epidermis* and *Candida albicans*.

2. Experimental

Notegeneral remarks, step by step identification of the phytochemical properties of barberry root extract and spectral data of the synthesized compounds are given in supplementary file.

2.1. Preparation of berberine from barberry root extract

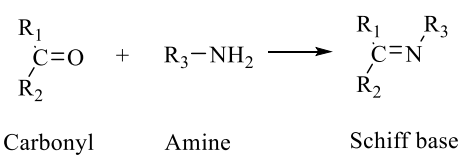
Barberry root was collected from Birjand, Iran. The roots were dried in the shade and powdered with a mechanical mill. Methanolic extract was prepared by soaking 150 g of root bark powder in 500 ml of methanol for 72 h. The extract was filtered through filter paper, and concentrated under the hood for 2 h. Finally, berberine chloride was obtained from concentrated extract.

2.2. Preparation of nitro-berberine chloride 2

Under stirring conditions at 0 °C, sodium nitrite (0.9 g) was added to a solution of berberine chloride **1** (1 g) in acetic acid (35 ml). Then, concentrated HNO_3 (1.5 ml) was added dropwise to it and stirred at 0 °C for another 5 min. The reaction mixture was heated at 50 °C for 1 h, before quenching by addition of water (30 ml), and extracted three times using a chloroform/methanol solution (v/v = 10:1). The organic layer ($CHCl_3$ phase) was concentrated under reduced pressure, and the residue was purified using a silica gel plate with a mixture of chloroform/methanol (v/v = 20:1) to yield a red solid.

2.3. Preparation of amino-berberine chloride 3

$SnCl_2{\cdot}2H_2O$ (0.43 g) and HCl (0.5 ml) were added to a flask containing ethanolic solution of nitrated berberine **2** (0.2 g; 8 ml), and the mixture was refluxed for 30 min. After completion of the reaction, the solvent was removed under reduced pressure. A 5 % NaOH aqueous solution was added dropwise to the residue to adjust the pH to 10. The resulting solution was extracted three times using *n*-butanol (3 × 20 ml). The organic layer was concentrated under reduced pressure, and the residue was purified using a silica gel plate with a mixture of chloroform/methanol (v/v = 15:1) to yield a red solid.



Scheme 1. General procedure for the formation of Schiff bases.

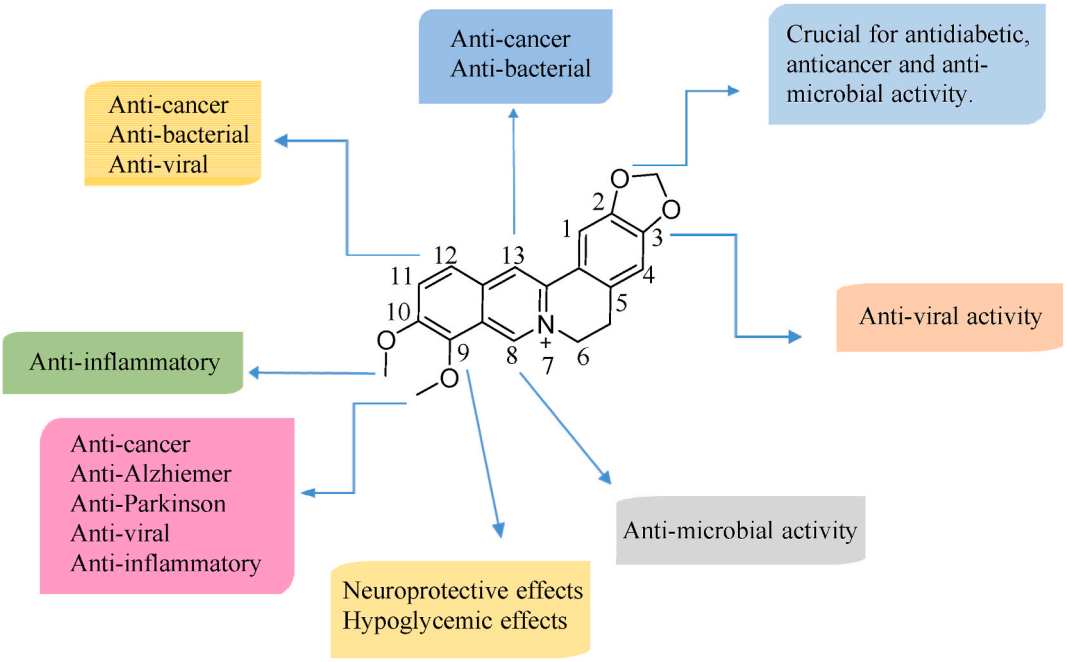


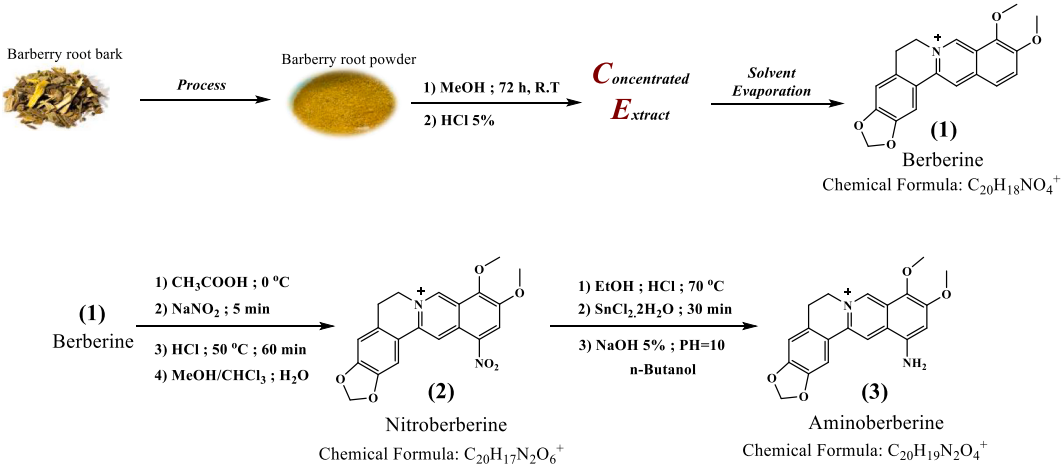
Fig. 1. Various sites for structural modification in berberine scaffold.

2.4. Preparation of berberine Schiff bases

0.5 mmol of benzaldehyde derivatives **4a-i** were added to a solution including amino-berberine **3** (0.5 mmol; 0.088 g) in 5 ml of ethanol, and the mixture was stirred at room temperature for 2 h. The obtained sediment was filtered and washed twice with ethanol to remove unreacted aldehydes. The solid was dried under room temperature for 24 h to achieve Schiff bases **5a-i**.

2.5. Biological testing

E. coli (PTCC 1399, ATCC 25922), *P. aeruginosa* (PTCC 1310. ATCC 10145), *K. pneumoniae* (PTCC 1290, NCTC 5056) and *A. baumannii* (PTCC 1855, ATCC BAA-747) as Gram-negative bacterial strains, *S. epidermidis* (PTCC 1435, ATCC 14990) and *S. pyogenes* (PTCC 1447, ATCC 12204) as Gram-positive bacterial strains and *C. albicans* (PTCC 5027, ATCC 10231) and *A. fumigatus* (PTCC 5009) as fungal strains were purchased from the Persian Type Culture Collection (PTCC), Karaj, Iran. DPPH free radical scavenging assay and disk diffusion susceptibility test were performed to determine IC_{50} (the half maximal inhibitory concentration) and inhibition zone



Scheme 2. Schematic of amino-berberine synthesis.

diameter (IZD) values, respectively [42,43]. In antimicrobial experiments, all derivatives were dissolved in DMSO to give initial concentrations of 10 mg ml^{-1}. The results of biological tests were expressed as the average of three independent experiments. Data were analyzed statistically by ANOVA and Tukey's tests at a significance level of P Value < 0.05 using the SPSS statistical software (version 22).

3. Results and discussion

Berberine is an important protoberberine isoquinoline alkaloid with various pharmacological activities such as antidiabetic, anticancer, antimicrobial, immunomodulatory, antitumor, and glucose- and cholesterol-lowering [44]. Chemical modification of natural products is an effective method to enhance their pharmaceutical activities [45]. To improve medicinal properties of berberine, it was extracted from barberry root, nitrated, reduced to a primary amine. Amino-berberine was then condensed with benzaldehyde derivatives to semi-synthesize new herbal Schiff bases (Scheme 2).

Phytochemical screening, structural characterization, reaction optimization, preparation of new derivatives, and antioxidant and antimicrobial examination of berberine and its functionalized derivatives were performed in this study. Methanolic, aqueous, and ethanolic extracts were separately prepared from barberry root by adding a specific amount of solvent to the sample and soaking at ambient temperature for 72 h. The extracts were filtered and used for phytochemical tests, and the results described in Table 1. The signs (+) and (−) indicate the presence or the absence of phytochemical compounds. According to the table, the methanolic extract had more secondary metabolites than the other two extracts, showing the presence of alkaloids, flavonoids, tannins, carbohydrates, phenols, and terpenes, and the absence of steroids, proteins, and anthocyanins.

Berberine and its nitrated and aminated derivatives were identified using FT-IR spectroscopy, which shown in Fig. 2. In FT-IR spectra, the broad absorption band at 1000-1300 cm^{-1} are attributed to stretching vibrations of C–N and C–O bonds, which are typical for alkaloids. In the spectrum of nitro-berberine (Fig. 1b), the symmetric and asymmetric strong absorption bands at 1362 cm^{-1} and 1506 cm^{-1} are attributed to NO_2 stretching vibrations. Meanwhile, in the spectrum of amino berberine (Fig. 1b), notable removal related to the nitro group and the absorptions of the amine group are observed in the region of 1602 cm^{-1} and 3224-3419 cm^{-1}. The amine group in the 1602 cm^{-1} and 3224-3419 cm^{-1} region overlaps with the functional groups of the berberine structure. Importantly, the peak intensity in this region is significantly higher compared to other spectra, which confirms the presence of the amine group in the berberine structure. The peaks observed at 1400–1450, 1655 and 2950-3120 cm^{-1} show stretching vibrations of aromatic C═C, C═N^+, and aliphatic/aromatic C–H bonds, respectively.

After characterizing aminoberberine, its activity in the conversion to a Schiff base was examined. Various parameters affecting this process were investigated, including solvent effects (H_2O, EtOH, CH_3CN, CH_2Cl_2, EtOH/H_2O), temperature (25–90 °C), and reaction time (15–120 min), as depicted in Figs. 4 and 5. To synthesize berberine Schiff bases under optimized conditions, a condensation reaction was conducted between 1 mmol of amino-berberine and 1 mmol of benzaldehyde, serving as the model reaction, in a 5 ml solvent at 50 °C (Fig. 3). Among the tested solvents, EtOH yielded the highest Schiff base yield.

Subsequently, temperature optimization (ranging from 25 to 90 °C) and time optimization (ranging from 15 to 120 min) were performed in EtOH (Fig. 4), confirming that room temperature (25 °C) was the optimal condition. Within the time range of 15–90 min, it was observed that prolonging the reaction time beyond 30 min did not significantly affect the synthesis of the Schiff base. Thus, the optimized conditions were determined as room temperature and a reaction time of 30 min.

Various berberine Schiff bases were prepared under the optimized conditions, as summarized in Table 2. No significant relationship was observed between the reactivity of benzaldehydes with berberine, only the lowest yields were obtained with both nitro-benzaldehyde derivatives **4c** and **4d**.

Free radicals scavenging ability of all products was studied against DPPH as a valid protocol (Fig. 5). Ascorbic acid (vitamin C, ASA) was used as control. Standard divisions of mean IC_{50} values were in the range of 0.28–4.43. Notable antioxidant effects were observed with berberine. Nitration and amination reduced these effects, in fact, the least effects were observed with nitro-berberine **2**. All Schiff bases derived from amino-berberine showed stronger effects than the original amine and their antioxidant properties were approximately equal to berberine. Among the Schiff bases, the increase in Schiff base **5g** containing 4-hydroxyphenyl substituent has been more significant. it was also the only compound more effective than berberine. Antioxidant capacity of Mannich bases piperazine linked berberine was determined *via* ABTS (2,2′-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid), DPPH and FRAP (ferric reducing ability of plasma) assays [46], their IC_{50} values against DPPH and ABTS free radicals were ranged in 12.17–23.86 and 4.644–12.96 μg ml^{-1}, respectively.

Blocking properties of all derivatives were evaluated against bacterial and fungal pathogens and expressed as IZD values in Fig. 6)

Table 1
Preliminary phytochemical investigation of barberry root extracts.

Phytochemical Test	Alkaloid	Terpenoid	Steroid	Tannin	Anthocyanin	Carbohydrate	Protein	Flavonoid	Total phenol
MEB	+	+	−	+	−	+	−	+	+
EEB	+	−	−	+	−	+	−	+	+
AEB	−	−	−	−	−	+	−	+	−

MEB: Methanolic extract of berberine; EEB: Ethanolic extract of berberine; AEB: Aqueous extract of berberine.
(+) indicates presence of constituents; (−) indicates absence of constituents.

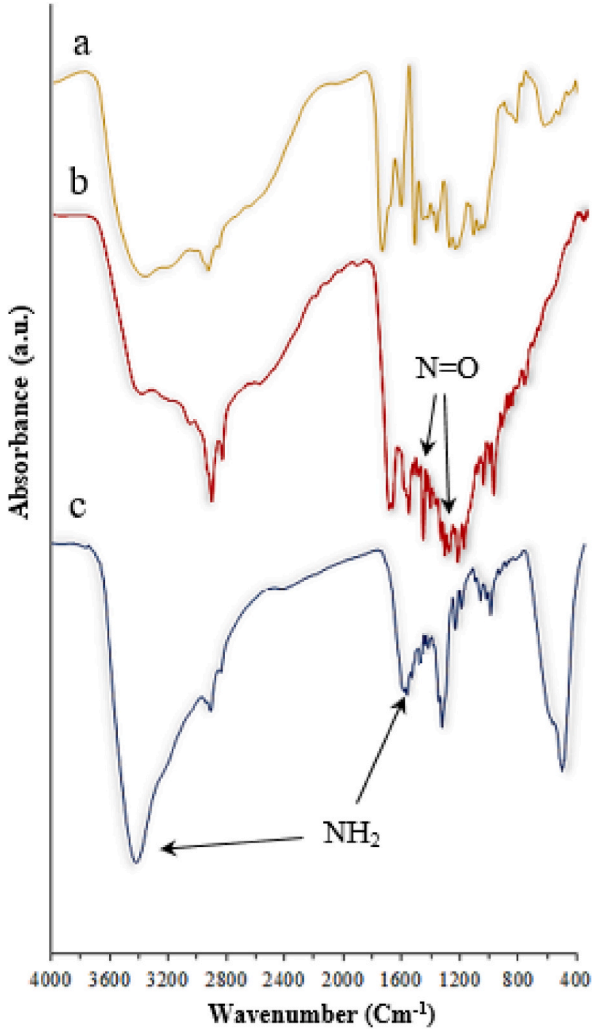


Fig. 2. FT-IR spectra of (a) berberine, (b) nitro-berberine, and (c) amino-berberine.

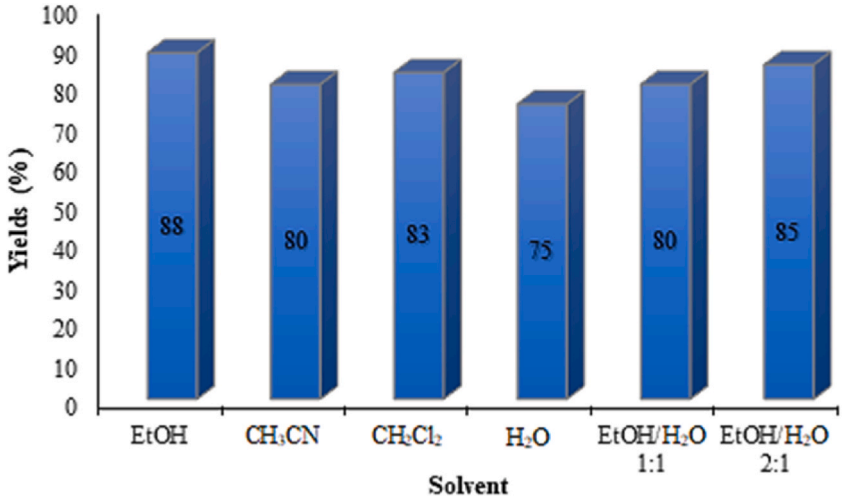


Fig. 3. Effect of solvent on the Schiff Base yield Reaction conditions: Amino-berberine (0.5 mmol), benzaldehyde (0.5 mmol), Solvent (5 ml), Temp. (50 °C), Time (120 min).

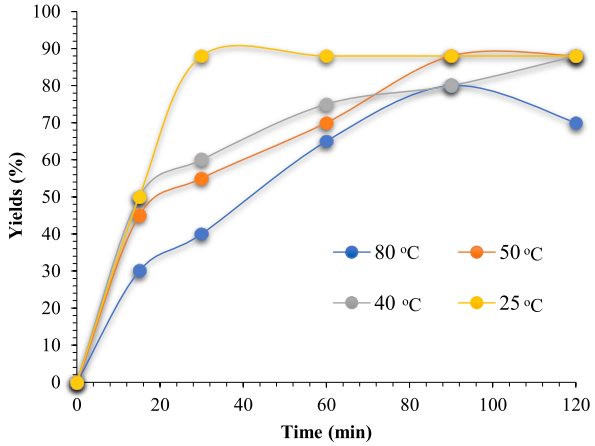


Fig. 4. Effect of temperature and time on the Schiff Base yield Reaction conditions: Amino-berberine (0.5 mmol), benzaldehyde (0.5 mmol), EtOH (5 ml).

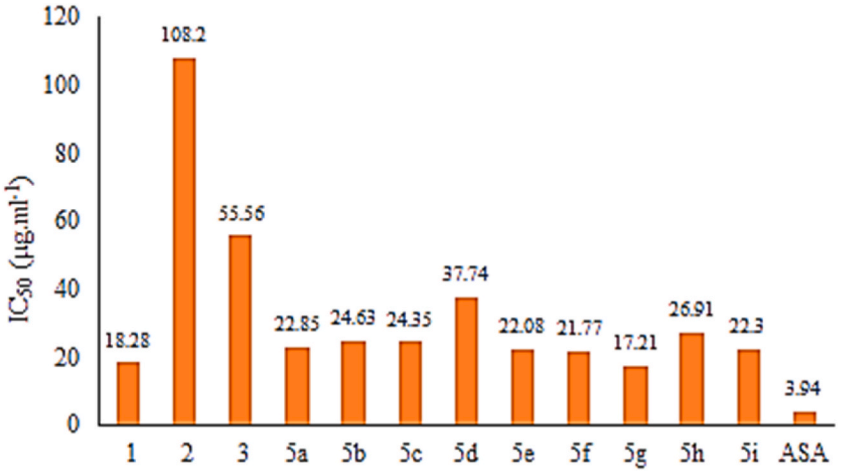
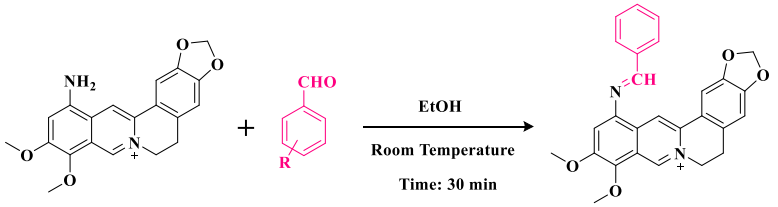


Fig. 5. DPPH free radical scavenging activity as an antioxidant indicator of berberine-based derivatives.

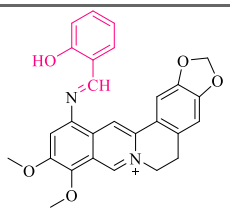
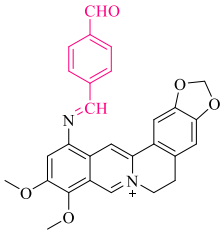
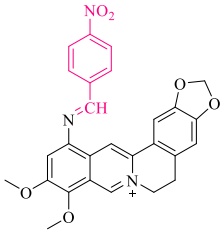
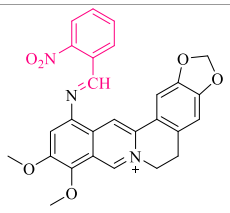
a-h(. Ceftriaxone (CFX) and ketoconazole (KTZ) were applied as antibiotic and antifungal drug, respectively. Standard divisions of mean IZD values were in the range of 1.17–3.62.

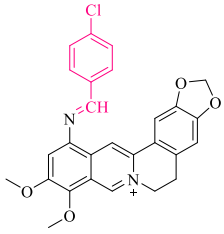
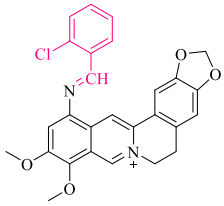
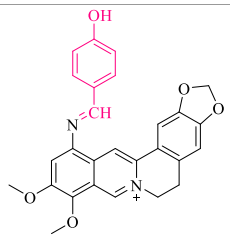
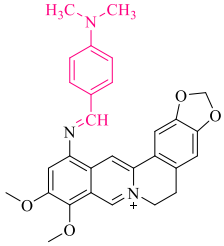
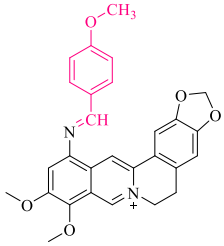
Nitro-berberine **2** could inhibit the growth of all tested microorganisms except *A. baumannii*. No blocking activity was observed against tested bacterial strains with berberine **1** and its aminated derivative **3**. Amino-berberine **3** could only inhibit the growth of two tested fungal strains. No antimicrobial effect was observed with Schiff bases **5e** and **5h**. Compounds including berberine **1** and Schiff bases **5a**, **5b**, **5e** were only effective on a microbial strain. Among the synthesized derivatives, nitro-berberine **2** and Schiff base **5c** were the only effective agents on *S. pyogenes* and *A. baumannii* strains, respectively. Tetrahydro protoberberine-based Schiff bases containing 1,2,4-triazole have been synthesized as potent antimicrobial agents [47]. Some of them showed better inhibitory activities than berberine, chloromycin, norfloxacin and fluconazole. Interaction of the most active derivative with MRSA DNA and calf thymus DNA was studied using molecular docking calculations and UV–Vis absorption spectroscopy to suggested its antibacterial action mechanism. It was suggested that it has dual-targeting antibacterial agent can inhibit the growth of bacteria by cleaving and/or intercalating bacterial DNA. A series of berberine-based Schiff bases containing 2-aminothiazolyl moieties were synthesized as inhibitory agents against some standard Gram-negative and Gram-positive bacterial strains as well as clinically drug-resistant *A. baumanii* with MICs ranged from 0.03 to 0.95 µM [48].

Table 2
Synthesis of berberine Schiff bases 5a-i.



[3] [4a-i] [5a-i]

Enty	Compound	R	Final structure	Yield (%)
1	5a	2-OH		88
2	5b	4-CHO		88
3	5c	4-NO_2		75
4	5d	2-NO_2		70

5	5e	4-Cl		83
6	5f	2-Cl		80
7	5g	4-OH		85
8	5h	4-N(Me)$_2$		83
9	5i	4-OMe		88

4. Conclusion

In this study, an attempt was made to semi-synthesize new derivatives based on the berberine natural product with possible enhanced antimicrobial and antioxidant properties. In this purpose, berberine was nitrated, aminated and condensed with a variety of benzaldehydes to produce the corresponding Schiff bases at yields 70–88 %. Nitrated berberine demonstrated the broad-spectrum antimicrobial activities, and all Schiff bases exhibited IC_{50} values $\leq$ 37.74 μg ml^{-1}, indicating their antioxidant potentials in preventing and/or eliminating oxidative stress. These findings suggest that the synthesized berberine-based derivatives are promising candidates for developing new antimicrobial and antioxidant agents. Compared to berberine-based derivatives, they are easily prepared and also have acceptable to interesting biological effects. According to the obtained results, the antioxidant and antimicrobial capacities of berberine will probably be improved through hydroxylation as well as nitration or chlorination, respectively.

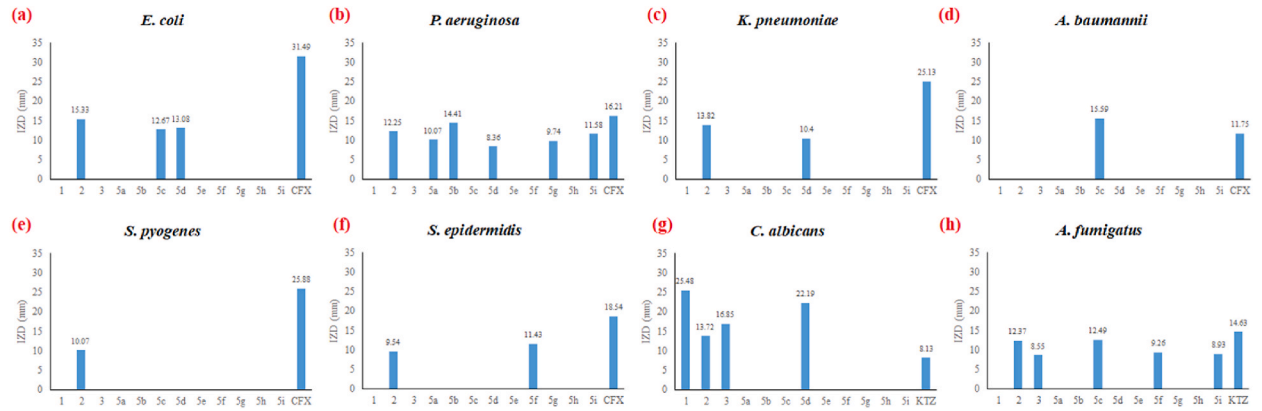


Fig. 6. Inhibition zone diameter as a measure of the antimicrobial activity of berberine-based derivatives. a–d: Gram-negative bacteria; e,f: Gram-positive bacteria; g,h: Fungi.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Soheila Alipour Noghabi: Writing - original draft, Investigation. **Pouya Ghamari kargar:** Writing - review & editing, Writing - original draft, Supervision, Data curation, Conceptualization. **Ghodsieh Bagherzade:** Supervision, Project administration, Methodology. **Hamid Beyzaei:** Writing - review & editing, Methodology, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22783.

References

[1] P. Ghamari kargar, G. Bagherzade, O. Bakhshi, Biosynthesis of organic nanocomposite using Pistacia Vera L. hull: an efficient antimicrobial agent, Medbiotech J 5 (2021) 41–48, https://doi.org/10.22034/MBT.2021.135222.

[2] F. Alam, K.M. Din, R. Rasheed, A. Sadiq, M.S. Jan, A.M. Minhas, A. Khan, Phytochemical investigation, anti-inflammatory, antipyretic and antinociceptive activities of Zanthoxylum armatum DC extracts-in vivo and in vitro experiments, Heliyon 6 (2020), e05571, https://doi.org/10.1016/j.heliyon.2020.e05571.

[3] O. Bakhshi, G. Bagherzade, P. Ghamari kargar, Biosynthesis of organic nanocomposite using pistacia vera L. Hull: an efficient antimicrobial agent, Bioinorgan. Chem. Appl. 2021 (2021) 1–18, https://doi.org/10.1155/2021/4105853.

[4] A. Kumar, S. Sreedharan, A.K. Kashyap, P. Singh, N. Ramchiary, A review on bioactive phytochemicals and ethnopharmacological potential of purslane (Portulaca oleracea L.), Heliyon 8 (2022), e08669, https://doi.org/10.1016/j.heliyon.2021.e08669.

[5] M. Moodi, P. Ghamari kargar, A. Nameni, G. Bagherzade, Examination of the chemical profile of methanolic extract of Agaricus bisporus wild edible mushroom, Zarnagh region (East Azerbaijan province, Iran), J. Hortic. Postharvest Res. 5 (2022) 1–12, https://doi.org/10.22077/jhpr.2021.4266.1204.

[6] S. Gaba, A. Saini, G. Singh, V. Monga, An insight into the medicinal attributes of berberine derivatives: a review, Bioorg. Med. Chem. 38 (2021), 116143, https://doi.org/10.1016/j.bmc.2021.116143.

[7] M. Zhang, J. Li, X. Guo, X. Wang, D. Shi, L. Cui, Y. Zhou, Co-administration of berberine/gypenosides/bifendate ameliorates metabolic disturbance but not memory impairment in type 2 diabetic mice, Heliyon 7 (2021), e06004, https://doi.org/10.1016/j.heliyon.2021.e06004.

[8] A.E. Abd El-Wahab, D.A. Ghareeb, E.E. Sarhan, M.M. Abu-Serie, M.A. El Demellawy, In vitro biological assessment of berberis vulgaris and its active constituent, berberine: antioxidants, anti-acetylcholinesterase, anti-diabetic and anticancer effects, BMC Compl. Alternative Med. 13 (2013) 218, https://doi.org/10.1186/1472-6882-13-218.

[9] K. Lin, S. Liu, Y. Shen, Q. Li, Berberine attenuates cigarette smoke-induced acute lung inflammation, Inflammation 36 (2013) 1079–1086, https://doi.org/10.1007/s10753-013-9640-0.

[10] F.S. Yu, J.S. Yang, H.J. Lin, C.S. Yu, T.W. Tan, Y.T. Lin, C.C. Lin, H.F. Lu, J.G. Chung, Berberine inhibits WEHI-3 leukemia cells in vivo, In Vivo 21 (2007) 407–412.

[11] M. Čerňáková, D. Košťálová, V. Kettmann, M. Plodová, J. Tóth, J. Dřímal, Potential antimutagenic activity of berberine, a constituent of Mahonia aquifolium, BMC Compl. Alternative Med. 2 (2002) 2, https://doi.org/10.1186/1472-6882-2-2.

[12] Z. Jiang, F. Liu, E.S. Ong, S.F.Y. Li, Metabolic profile associated with glucose and cholesterol lowering effects of berberine in Sprague–Dawley rats, Metabolomics 8 (2012) 1052–1068, https://doi.org/10.1007/s11306-012-0407-7.

[13] S.K. Kulkarni, A. Dhir, Berberine: a plant alkaloid with therapeutic potential for central nervous system disorders, Phyther. Res. 24 (2010) 317–324, https://doi.org/10.1002/ptr.2968.

[14] R. Domitrović, H. Jakovac, G. Blagojević, Hepatoprotective activity of berberine is mediated by inhibition of TNF-α, COX-2, and iNOS expression in CCl_4-intoxicated mice, Toxicology 280 (2011) 33–43, https://doi.org/10.1016/j.tox.2010.11.005.

[15] Y. Feng, K.-Y. Siu, X. Ye, N. Wang, M.-F. Yuen, C.-H. Leung, Y. Tong, S. Kobayashi, Hepatoprotective effects of berberine on carbon tetrachloride-induced acute hepatotoxicity in rats, Chin. Med. 5 (2010) 33, https://doi.org/10.1186/1749-8546-5-33.

[16] A. Hermenean, C. Popescu, A. Ardelean, M. Stan, N. Hadaruga, C.-V. Mihali, M. Costache, A. Dinischiotu, Hepatoprotective effects of berberis vulgaris L. Extract/β cyclodextrin on carbon tetrachloride–induced acute toxicity in mice, Int. J. Mol. Sci. 13 (2012) 9014–9034, https://doi.org/10.3390/ijms13079014.

[17] Q. Tang, P. Wang, H. Liu, D. Jin, X. Chen, L. Zhu, Effect of chlorantraniliprole on soil bacterial and fungal diversity and community structure, Heliyon 9 (2023), e13668, https://doi.org/10.1016/j.heliyon.2023.e13668.

[18] T.X. Vu, T.B. Tran, M.B. Tran, T.T.K. Do, L.M. Do, M.T. Dinh, H.-D. Thai, D.-N. Pham, V.-T. Tran, Efficient control of the fungal pathogens Colletotrichum gloeosporioides and Penicillium digitatum infecting citrus fruits by native soilborne Bacillus velezensis strains, Heliyon 9 (2023), e13663, https://doi.org/10.1016/j.heliyon.2023.e13663.

[19] B. Vhanale, D. Kadam, A. Shinde, Synthesis, spectral studies, antioxidant and antibacterial evaluation of aromatic nitro and halogenated tetradentate Schiff bases, Heliyon 8 (2022), e09650, https://doi.org/10.1016/j.heliyon.2022.e09650.

[20] M. Abbas, T. Hussain, M. Arshad, A.R. Ansari, A. Irshad, J. Nisar, F. Hussain, N. Masood, A. Nazir, M. Iqbal, Wound healing potential of curcumin cross-linked chitosan/polyvinyl alcohol, Int. J. Biol. Macromol. 140 (2019) 871–876, https://doi.org/10.1016/j.ijbiomac.2019.08.153.

[21] P. Ghamari kargar, G. Bagherzade, H. Beyzaei, S. Arghavani, BioMOF-Mn: an antimicrobial agent and an efficient nanocatalyst for domino one-pot preparation of xanthene derivatives, Inorg. Chem. (2022), https://doi.org/10.1021/acs.inorgchem.2c00819.

[22] S.G. Nayak, B. Poojary, Synthesis of novel Schiff bases containing arylpyrimidines as promising antibacterial agents, Heliyon 5 (2019), e02318, https://doi.org/10.1016/j.heliyon.2019.e02318.

[23] W. Qin, S. Long, M. Panunzio, S. Biondi, Schiff bases: a short survey on an evergreen chemistry tool, Molecules 18 (2013) 12264–12289, https://doi.org/10.3390/molecules181012264.

[24] M.J. Barnabas, S. Parambadath, S. Nagappan, C.-S. Ha, Sulfamerazine Schiff-base complex intercalated layered double hydroxide: synthesis, characterization, and antimicrobial activity, Heliyon 5 (2019), e01521, https://doi.org/10.1016/j.heliyon.2019.e01521.

[25] K.P. Rakesh, H.K. Kumara, B.J. Ullas, J. Shivakumara, D. Channe Gowda, Amino acids conjugated quinazolinone-Schiff's bases as potential antimicrobial agents: synthesis, SAR and molecular docking studies, Bioorg. Chem. 90 (2019), 103093, https://doi.org/10.1016/j.bioorg.2019.103093.

[26] A. Sethiya, D. Joshi, A. Manhas, N. Sahiba, D.K. Agarwal, P.C. Jha, S. Agarwal, Glycerol based carbon sulfonic acid catalyzed synthesis, in silico studies and in vitro biological evaluation of isonicotinohydrazide derivatives as potent antimicrobial and anti-tubercular agents, Heliyon 9 (2023), e13226, https://doi.org/10.1016/j.heliyon.2023.e13226.

[27] N.N.M. Shahri, H. Taha, M.H.S.A. Hamid, E. Kusrini, J.-W. Lim, J. Hobley, A. Usman, Antimicrobial activity of silver sulfide quantum dots functionalized with highly conjugated Schiff bases in a one-step synthesis, RSC Adv. 12 (2022) 3136–3146, https://doi.org/10.1039/D1RA08296E.

[28] P. Ghamari Kargar, S. Aryanejad, G. Bagherzade, Simple synthesis of the novel Cu-MOF catalysts for the selective alcohol oxidation and the oxidative cross-coupling of amines and alcohols, Appl. Organomet. Chem. 34 (2020), https://doi.org/10.1002/aoc.5965.

[29] A.F. Abdel-Magid, K.G. Carson, B.D. Harris, C.A. Maryanoff, R.D. Shah, Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures 1, J. Org. Chem. 61 (1996) 3849–3862, https://doi.org/10.1021/jo960057x.

[30] T.Y. Fonkui, M.I. Ikhile, D.T. Ndinteh, P.B. Njobeh, Microbial activity of some heterocyclic Schiff bases and metal complexes: a review, Trop. J. Pharmaceut. Res. 17 (2019) 2507, https://doi.org/10.4314/tjpr.v17i12.29.

[31] H. Khashei Siuki, P. Ghamari Kargar, G. Bagherzade, New Acetamidine Cu(II) Schiff base complex supported on magnetic nanoparticles pectin for the synthesis of triazoles using click chemistry, Sci. Rep. 12 (2022) 3771, https://doi.org/10.1038/s41598-022-07674-7.

[32] P. Ghamari Kargar, A. Ravanjamjah, G. Bagherzade, A novel water-dispersible and magnetically recyclable nickel nanoparticles for the one-pot reduction-Schiff base condensation of nitroarenes in pure water, J. Chin. Chem. Soc. (Taipei, Taiwan) 68 (2021) 1916–1933, https://doi.org/10.1002/jccs.202100172.

[33] P. Ghamari kargar, G. Bagherzade, H. Beyzaei, A porous metal-organic framework (Ni-MOF): an efficient and recyclable catalyst for cascade oxidative amidation of alcohols by amines under ultrasound-irradiations, Mol. Catal. 526 (2022), 112372, https://doi.org/10.1016/j.mcat.2022.112372.

[34] T.T. Tidwell, Hugo (ugo) Schiff, Schiff bases, and a century of β-lactam synthesis, Angew. Chem., Int. Ed. 47 (2008) 1016–1020, https://doi.org/10.1002/anie.200702965.

[35] V. Milata, A. Svedova, Z. Barbierikova, E. Holubkova, I. Cipakova, D. Cholujova, J. Jakubikova, M. Panik, S. Jantova, V. Brezova, L. Cipak, Synthesis and anticancer activity of novel 9-O-substituted berberine derivatives, Int. J. Mol. Sci. 20 (2019) 2169, https://doi.org/10.3390/ijms20092169.

[36] K. Xiong, J. Deng, T. Yue, W. Hu, X. Zeng, T. Yang, T. Xiao, Berberine promotes M2 macrophage polarisation through the IL-4-STAT6 signalling pathway in ulcerative colitis treatment, Heliyon 9 (2023), e14176, https://doi.org/10.1016/j.heliyon.2023.e14176.

[37] Z.-J. Huang, Y. Zeng, P. Lan, P.-H. Sun, W.-M. Chen, Advances in structural modifications and biological activities of berberine: an active compound in traditional Chinese medicine, Mini-Rev. Med. Chem. 11 (2011) 1122–1129, https://doi.org/10.2174/138955711797655362.

[38] C.-Y. Lo, L.-C. Hsu, M.-S. Chen, Y.-J. Lin, L.-G. Chen, C.-D. Kuo, J.-Y. Wu, Synthesis and anticancer activity of a novel series of 9-O-substituted berberine derivatives: a lipophilic substitute role, Bioorg. Med. Chem. Lett. 23 (2013) 305–309, https://doi.org/10.1016/j.bmcl.2012.10.098.

[39] S. Zhang, X. Wang, W. Yin, Z. Liu, M. Zhou, D. Xiao, Y. Liu, D. Peng, Synthesis and hypoglycemic activity of 9-O-(lipophilic group substituted) berberine derivatives, Bioorg. Med. Chem. Lett. 26 (2016) 4799–4803, https://doi.org/10.1016/j.bmcl.2016.08.027.

[40] H.-X. Cui, Y.-N. Hu, J.-W. Li, K. Yuan, Y. Guo, Preparation and evaluation of antidiabetic agents of berberine organic acid salts for enhancing the bioavailability, Molecules 24 (2018) 103, https://doi.org/10.3390/molecules24010103.

[41] H.-K. Hsu, K.-H. Hsu, Y.-M. Cheng, H.-Y. Suen, S.-F. Peng, Development and in vitro evaluation of linear PEI-shelled heparin/berberine nanoparticles in human osteosarcoma U_2O_S cells, Molecules 23 (2018) 3121, https://doi.org/10.3390/molecules23123121.

[42] H. Beyzaei, M. Moghaddam-Manesh, R. Aryan, B. Ghasemi, A. Samzadeh-Kermani, Synthesis and in vitro antibacterial evaluation of 6-substituted 4-amino-pyrazolo[3,4-d]pyrimidines, Chem. Pap. 71 (2017) 1685–1691, https://doi.org/10.1007/s11696-017-0163-2.

[43] H. Beyzaei, M. Kamali Deljoo, R. Aryan, B. Ghasemi, M.M. Zahedi, M. Moghaddam-Manesh, Green multicomponent synthesis, antimicrobial and antioxidant evaluation of novel 5-amino-isoxazole-4-carbonitriles, Chem. Cent. J. 12 (2018) 114, https://doi.org/10.1186/s13065-018-0488-0.

[44] W. Cai, Z, C. Wang, Yang, Role of Berberine in Alzheimer's Disease, Neuropsychiatr. Dis. Treat., 2016, pp. 2509–2520.

[45] D. Xiao, Z. Liu, S. Zhang, M. Zhou, F. He, M. Zou, J. Peng, X. Xie, Y. Liu, D. Peng, Berberine derivatives with different pharmacological activities via structural modifications, Mini-Rev. Med. Chem. 18 (2018) 1424–1441, https://doi.org/10.2174/1389557517666170321103139.

[46] B. Mistry, R.V. Patel, Y.-S. Keum, D.H. Kim, Synthesis of N-Mannich bases of berberine linking piperazine moieties revealing anticancer and antioxidant effects, Saudi J. Biol. Sci. 24 (2017) 36–44, https://doi.org/10.1016/j.sjbs.2015.09.005.
[47] J.-R. Duan, H.-B. Liu, P. Jeyakkumar, L. Gopala, S. Li, R.-X. Geng, C.-H. Zhou, Design, synthesis and biological evaluation of novel Schiff base-bridged tetrahydroprotoberberine triazoles as a new type of potential antimicrobial agents, Medchemcomm 8 (2017) 907–916, https://doi.org/10.1039/C6MD00688D.
[48] W.-W. Gao, L. Gopala, R.R.Y. Bheemanaboina, G.-B. Zhang, S. Li, C.-H. Zhou, Discovery of 2-aminothiazolyl berberine derivatives as effectively antibacterial agents toward clinically drug-resistant Gram-negative Acinetobacter baumanii, Eur. J. Med. Chem. 146 (2018) 15–37, https://doi.org/10.1016/j.ejmech.2018.01.038.