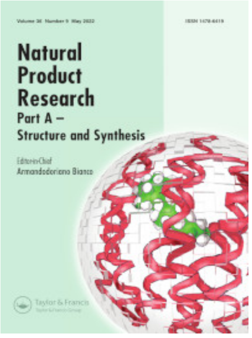

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Natural Product Research
Formerly Natural Product Letters

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gnpl20

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To cite this article: G. Lakshmanan, R. Selvam, Ammar. B. Altemimi, Alberto Baldelli, A. R. Bharathi, B. Gopalakrishnan, L. Karthik, D. Saravanan, M. Kavitha, Muthanna J. Mohammed, Francesco Cacciola, G. Jayalakshmi & Anubhav Pratap-Singh (2022): Phytochemical screening of ethanolic extracts of *Cuminum cyminum* L. seeds along with the evaluation of antidiabetic properties by molecular docking approach, Natural Product Research, DOI: 10.1080/14786419.2022.2078973

To link to this article: https://doi.org/10.1080/14786419.2022.2078973

NATURAL PRODUCT RESEARCH
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SHORT COMMUNICATION

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Phytochemical screening of ethanolic extracts of *Cuminum cyminum* L. seeds along with the evaluation of antidiabetic properties by molecular docking approach

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ABSTRACT

In this contribution, ethanolic extracts of *Cuminum cyminum* (*C. cyminum*) seeds were evaluated in terms of phytochemical content, total phenol and flavonoid contents. As far as the analytical techniques are concerned, UV–Vis, FTIR, HPLC, NMR (1H and ^{13}C) and ESI-MS were performed. The binding capacity of five different antidiabetic enzymes was tested by *in silico* molecular docking studies. The HPLC, UV–Vis, FTIR, NMR and ESI-MS data highlighted the presence of seven biologically active molecules e.g. α-pinene, β-pinene, Δ^3-carene, ρ-cymene, α-terpineol, cuminaldehyde and linalool. The results coming from the *in silico* molecular docking studies showed that such phytochemicals present in the cumin seed extracts play an important role in the activity of key enzymes involved in carbohydrate metabolism. Therefore, *C. cyminum* is proven to be useful for the treatment of diabetes mellitus and its major secondary complications.

ARTICLE HISTORY
Received 5 April 2022
Accepted 13 May 2022

KEYWORDS
Antidiabetic enzymes; Cuminum cyminum; ESI; FTIR; HPLC; in silico

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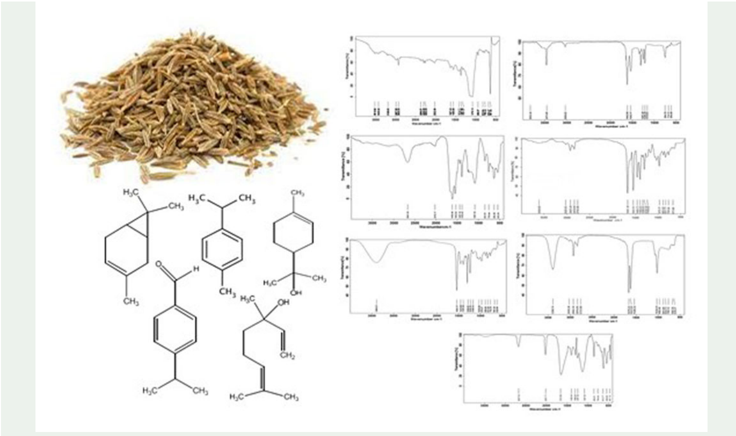
Supplemental data for this article can be accessed online at https://doi.org/10.1080/14786419.2022.2078973.



1. Introduction

Diabetes mellitus is a chronic metabolic disorder related to insulin deficiency. This type of diabetes is widely spread worldwide and affects more than 95% of the diabetic population (Singh et al. 2019). In order to maintain normoglycaemia in diabetic subjects, such as increasing insulin secretion, de-creasing insulin resistance, regulation of gluconeogenesis and glycogenosis and slowing down glucose absorption in the intestine, drugs employing several mechanisms of action are available on the market. However, these drugs do present two main disadvantages: undesirable side effects and resistance after continuous use. As a consequence, alternative medicines, showing a high efficiency with minimal side effects, are nowadays being researched by researchers in various fields. Surely, one of the most investigated alternative medicines is represented by plants. The targets of plant extracts can be different according to the plant properties. Applications of plant extracts have involved the treatment of diabetes (Allaq et al. 2020), but also antioxidant, hepatoprotective, antimicrobial, anticancer, analgesic, wound healing and ulcer antidiabetes activities from different plant extracts (Jarzębski et al. 2020).

Cuminum cyminum L. (*C. cyminum*), usually known as cumin or zeera, is an annual, diploid cross-pollinated herbaceous flowering and grassy plant belonging to the family Apiaceae. It is distributed in several parts of the world, including South East Asian countries like India, Pakistan etc., Mediterranean countries, such as Egypt, Turkey, Spain, and Morocco and Asian countries, such as China or Central American nations, such as Mexico (Mortazavian et al. 2018). In all of these countries, this seed spice has been used not only in the food industry, but also in the pharmaceutical one, due to the presence of organic acids and phytochemicals (Al-Snafi 2016). In the Indian traditional medicine, the seeds are widely used for their therapeutic efficacies on gastrointestinal, gynaecological, respiratory disorders, toothache, diarrhoea, epilepsy, arthritis and hypercholesterolemia. Decoctions, made out of the *C. cyminum* seeds, have been extensively used in Indian traditional medicine to maintain normoglycaemia as well as to control the levels of lipid profile. Several reports have highlighted various pharmacological activities e.g. antibacterial, anticancer, antidiabetic, antiulcer, larvicidal, hepatoprotective, antioxidant and immunomodulatory, anti-inflammatory, antifungal effects. If extracted, the cumin seeds might show hypoglycaemic effects (Dhandapani et al. 2002). Furthermore, the antimicrobial properties of these seeds have been proven and correlated to the active phytochemicals such as cuminaldehyde, eugenol and β-pinene (Johri 2011). Even when administrated orally and simply diluted in water, cumin extract was proved to reduce blood glucose, cholesterol, free fatty acid, triglyceride levels in plasma and liver tissues, and glycosylated haemoglobin levels for the control of the body-weight of diabetic rats (Willatgamuwa et al. 1998). Notably, such effects are enhanced after the third week of administration (Ahmed 2017).

In the light of the above literature data concerning the antidiabetic properties of cumin seeds, in this work, the major phytochemicals present in the *C. cyminum* seeds extracts were identified by HPLC coupled to diode-array detection (DAD). Afterwards, the individual lead molecules were characterized by FTIR and ESI-MS detection. The efficacy of the isolated phytochemicals in ameliorating secondary complications such as diabetic retinopathy, glycogen metabolism and gluconeogenesis was investigated, hereby for the first time, by *in silico* molecular docking studies.

2. Results and discussion

2.1. Phytochemical screening

The phytochemical screening, performed according to established procedures, discovered the occurrence of biologically active phytoconstituents, such as alkaloids, flavonoids, saponins, tannins, phytosterols, triterpenoids, phenolic compounds and glycosides, in the ethanolic extract of *C. cyminum* seeds (Table S1). In addition, the total phenolic, total flavonoids, carbohydrate and protein content was also determined; notably values as high 6.28 ± 0.86 mg gallic acid equivalents/g and 9.05 ± 0.16 mg quercetin equivalents/g were attained for total phenolic content and total flavonoid content, respectively (Table S2).

2.2. HPLC analysis

The HPLC data highlighted the presence of seven biologically active molecules *viz.* α–pinene, β-pinene, Δ^3-carene, ρ-cymene, α-terpineol, cuminaldehyde and linalool (Figure S1). Based on the retention time, the individual phytochemicals were identified and further confirmed by respective reference standards. The physicochemical parameters such as molecular formula, molecular weight, molecular structure and retention time of the individual phytochemicals are presented in Table S3.

Cuminaldehyde, γ-terpinene, o-cymene, limonene and β-pinene are indicated as the main components of *C. cyminum* seeds (Rihawy et al. 2014; Farvardin et al. 2017). Previous references reported that in cumin seeds of Egyptian cultivars, the main components are cuminaldehyde (35.25%), tetradecane (12.25%), γ-terpinene (12%), β-ocimene (9.72%), p-mentha-2-en-ol (9%), α-terpinyl acetate (5.32%), α-terpinolene (3%), limonine (0.5%), myrcene (0.2%), β-pinene (0.9%) and α-pinene (0.19%) (Jalali-Heravi et al. 2007). A different variety can show slightly different ratios of the main components. For example, the Tunisian variety of *C. cyminum* does contain cuminaldehyde

(39.48%), γ-terpinene (15.21%), o-cymene (11.82%), β-pinene (11.13%), 2-caren-10-al (7.93%), t-carveol (4.49%) and myrtenal (3.5%) (Hajlaoui et al. 2010). Notably, the data attained in this study are in agreement with the previous published reports (Agarwal et al. 2017).

2.3. Spectral analysis of the isolated molecules

See supplementary material.

2.4. Molecular Docking studies

The data obtained in Table S4 through the *in silico* approach portraits the possible interactions between the phytochemicals present in the seeds extracts and the target receptors such as hexokinase, PEPCK and glycogen phosphorylase. The data also provide the rationale for the use of cumin seeds in the treatment of diabetes and its secondary complications.

2.4.1. Hexokinase (HK-EC: 2.7.1.1)

The activity of hexokinase is drastically decreased in type-I diabetic patients because of the absolute lack of insulin secretion in the pancreatic beta cells. Similarly, due to the insufficiency coupled with insulin resistance, the activity of hexokinase is decreased in type–II diabetic patients. In view of the above, in the present study an attempt has been made to determine the affinity of the isolated phytochemicals towards hexokinase by *in silico* methods. The affinity in terms of binding energy revealed that the phytochemicals namely α-Terpineol and Linalool do have a significant stimulatory effect on the activity of hexokinase. Thus, it may be concluded that α-Terpineol and Linalool which are present in the cumin seeds extracts are capable of controlling chronic hyperglycemia in diabetes by stimulating the activity of hexokinase (Table S4 and Figure S4).

2.4.2. Phosphoenolpyruvate carboxykinase (PEPCK)

The interaction between the major phytochemicals occurring in the cumin seeds extract towards the PEPCK is presented in Figure S5. From the data obtained, it is evident that phytochemicals such as α-Terpineol, Cuminaldehyde and Linalool shows significant affinity towards PEPCK which is evident from the binding energy. It is further assumed that the above phytochemicals are capable of controlling chronic hyperglycaemic in diabetes through the negative regulation of gluconeogenesis by inhibiting activity of PEPCK. There are several reports in the literature evidencing that the phytochemicals present in the medicinal plants regulate the process of gluconeogenesis by inhibiting the activity of PEPCK. It is our hope that the *in silico* findings on the inhibitory role of PEPCK by the phytochemicals present in the cumin seeds may pave a role in the designing of new agents for maintaining normoglycaemia in T2DM patients.

2.4.3. Glycogen phosphorylase: (GP-EC: 2.4.1.1)

In this study, the phytochemicals extracted from the cumin seeds were examined for their modulatory effect on the activity of glycogen phosphorylase *in silico*. From the obtained it may be concluded that the major phytochemicals such as α-terpineol, cuminaldehyde and linalool are known to possess significant affinity towards glycogen phosphorylase which is evident from the binding energy obtained through *in silico* docking studies (Table S4 and Figure S6).

The results of the *in silico* molecular docking studies evidenced the possible regulatory role of the phytochemicals present in the cumin seeds extracts on the activity of key enzymes involved in carbohydrate metabolism. The binding energy obtained through the molecular docking studies represents the efficacy of the individual phytochemicals (lig-ands) towards the target enzymes (receptors). Future applications of these results will invite novel research into strategies for enhancing administration of plant extracts for nutraceutical and pharmaceutical applications.

3. Experimental

See supplementary material.

4. Conclusions

In this contribution, the ethanolic extracts of the seeds of *C. cyminum* were screened for the evaluation of their potential pharmacological and therapeutic effects Interestingly, the HPLC, UV–Vis, FTIR, NMR and ESI-MS data highlighted the presence of seven biologically active molecules e.g. α-pinene, β-pinene, Δ^3-carene, ρ-cymene, α-terpineol, cuminaldehyde and linalool. *In silico* molecular docking studies assessed their role in the activity of key enzymes involved in carbohydrate metabolism. The results of this study provide scientific evidence for the use of *C. cyminum* for the treatment of diabetes mellitus and its major secondary complications

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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