ISSN 2220-3192 (online)

World Journal of *Pharmacology*

World J Pharmacol 2023 December 22; 12(4): 35-52

Published by Baishideng Publishing Group Inc

World Journal of Pharmacology

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Continuous Publication Volume 12 Number 4 December 22, 2023

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ABOUT COVER

Editorial Board Member of *World Journal of Pharmacology*, Arvind K Goyal, PhD, Assistant Professor, Department of Biotechnology, Bodoland University, Debargaon, Kokrajhar- 783370, Bodoland Territorial Region, Assam, India. arvindkgoyal@buniv.edu.in

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INDEXING/ABSTRACTING

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NAME OF JOURNAL
World Journal of Pharmacology

ISSN
ISSN 2220-3192 (online)

LAUNCH DATE
February 9, 2012

FREQUENCY
Continuous Publication

EDITORS-IN-CHIEF
Pharkphoom Panichayupakaranant, Ahmed M Kabel, Muhammad Shahzad

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3192/editorialboard.htm

PUBLICATION DATE
December 22, 2023

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World J Pharmacol 2023 December 22; 12(4): 35-52

DOI: 10.5497/wjp.v12.i4.35

ISSN 2220-3192 (online)

ORIGINAL ARTICLE

Basic Study

Natural isothiocyanates of the genus *Capparis* as potential agonists of apoptosis and antitumor drugs

Lumír Hanuš, Tuvia Naor, Tatyana Gloriozova, Valery M Dembitsky

Specialty type: Pharmacology and pharmacy

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gupta S, Brazil; Zhang J, China

Received: August 28, 2023
Peer-review started: August 28, 2023
First decision: September 19, 2023
Revised: October 12, 2023
Accepted: November 24, 2023
Article in press: November 24, 2023
Published online: December 22, 2023

Lumír Hanuš, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, Hebrew University, Ein Kerem Campus, Jerusalem 91120, Israel

Tuvia Naor, Food Chemistry, Kibbutz, Yotvata 8882000, Israel

Tatyana Gloriozova, Department of Bioinformatics, Institute of Biomedical Chemistry, Moscow 119121, Russia

Valery M Dembitsky, Centre for Applied Research and Innovation, Lethbridge College, Lethbridge AB T1K 1L6, Canada

Corresponding author: Lumír Hanuš, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, Hebrew University, Ein Kerem Campus, Jerusalem 91120, Israel.
lumirh@ekmd.huji.ac.il

Abstract

BACKGROUND

Using gas chromatography-mass spectrometry (GC/MS) analysis, we examined the composition of volatile components present in the yellow and green fruits, seeds, and jam of the scrambling shrub *Capparis cartilaginea* (*C. cartilaginea*). These plant samples were collected from Kibbutz Yotvata in Israel. In all the tested samples, isothiocyanates were identified. Utilizing the PASS program, we ascertained the biological activity of these isothiocyanates present in the *Capparis* genus. The study results highlighted that all isothiocyanates could potentially act as apoptosis agonists, making them strong candidates for antitumor drugs. This information holds significant value for the fields of medicinal chemistry, pharmacology, and practical medicine.

AIM

To investigate the volatile components present in the yellow and green fruits, seeds, and jam of the *C. cartilaginea* shrub using GC/MS analysis, to detect isothiocyanates in all the analyzed plant samples, and to assess the biological activity of these isothiocyanates utilizing the PASS program.

METHODS

We utilized two primary methods to analyze the volatile compounds present in the yellow and green fruits, seeds, and jams of the *C. cartilaginea*, native to Israel. We identified biologically active isothiocyanates in these samples. Their antici-

pated biological activities were determined using the PASS program, with the most dominant activities being apoptosis agonist, anticarcinogenic, and antineoplastic specifically for genitourinary cancer.

RESULTS

Fruits, seeds, and jams containing isothiocyanates, which exhibit antineoplastic and anticarcinogenic activities, could be suggested for cancer prevention and management. Specific isothiocyanates, with therapeutic potential in this realm, could be recommended as potent anticancer agents in practical medicine following clinical trials.

CONCLUSION

The discovery that isothiocyanates exhibit potent antineoplastic and anticarcinogenic activities was unexpected. Additionally, certain isothiocyanates demonstrated antifungal, antiviral (specifically against arbovirus), and antiparasitic properties.

Key Words: *Capparis cartilaginea*; Fruits; Seeds; Isothiocyanates; Apoptosis; Anticancer

Core Tip: Using gas chromatography-mass spectrometry analysis, we examined the composition of volatile components present in the yellow and green fruits, seeds, and jam of the scrambling shrub *Capparis cartilaginea*. Fruits, seeds, and jams containing isothiocyanates, which exhibit antineoplastic and anticarcinogenic activities, could be suggested for cancer prevention and management. Specific isothiocyanates, with therapeutic potential in this realm, could be recommended as potent anticancer agents in practical medicine following clinical trials.

Citation: Hanuš L, Naor T, Gloriozova T, Dembitsky VM. Natural isothiocyanates of the genus *Capparis* as potential agonists of apoptosis and antitumor drugs. *World J Pharmacol* 2023; 12(4): 35-52
URL: https://www.wjgnet.com/2220-3192/full/v12/i4/35.htm
DOI: https://dx.doi.org/10.5497/wjp.v12.i4.35

INTRODUCTION

The genus *Capparis*, part of the Capparidaceae family, comprises approximately 250 species[1-3]. The Cartilage caper is notably prevalent across tropical and subtropical regions in Asia, America, and Africa[4-6]. Recent findings suggest that the genus *Capparis* encompasses about 400 compounds, including glycosides, glucosinolates, flavonoids, terpenoids, tannins, steroids, and isothiocyanates[7,8]. There is substantial evidence indicating the therapeutic potential of these phytochemicals in treating and preventing various ailments such as inflammation, cancer, bacterial infections, ulcers, and diabetes[9-11].

This study explored the volatile compounds present in the yellow and green fruits, seeds, and jam of *Capparis cartilaginea* (*C. cartilaginea*), a species native to Israel. Furthermore, we were keen to examine the distribution of isothiocyanates in the essential oils of the *Capparis* genus from various global regions. Included is a table detailing the isothiocyanates identified within the *Capparis* genus, along with their anticipated biological activities as determined using the PASS software.

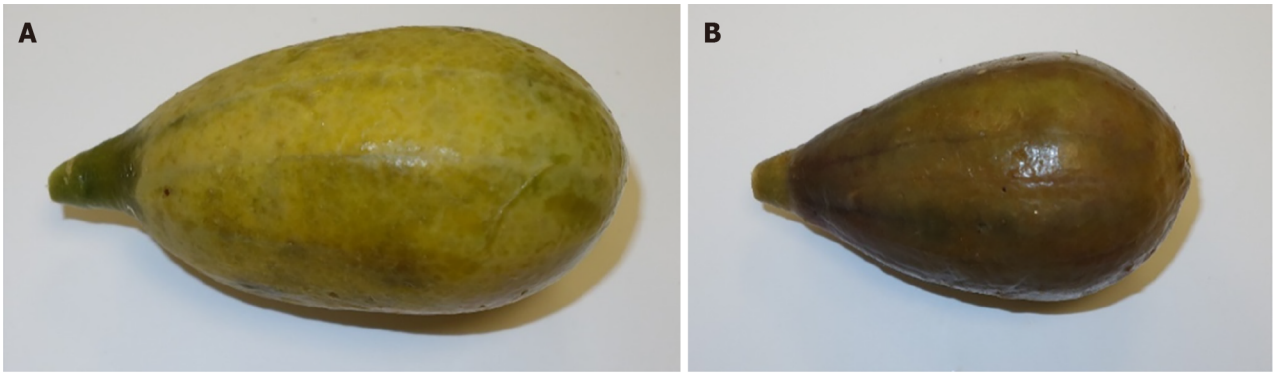
MATERIALS AND METHODS

Plant materials and extraction

The scrambling shrub *C. cartilaginea*, grown in Kibbutz Yotvata in Israel, was the source of the yellow and green fruits (Figure 1) harvested in 2019 for component analysis. The aromatic, juicy pulp of the fruit was available at the Kibbutz store, labeled as "*Jam of Tuvia Naor*". Samples were taken from shrubs reaching heights of up to 3 meters. The fruit is globose-ellipsoid in shape, with a reddish hue, measuring (3-6) cm × (1.6-4) cm. Fresh biological materials underwent head space and solid phase microextraction gas chromatography-mass spectrometry (GC-MS) analysis, following the methods that we have previously detailed[12-14].

General experimental procedures

For the GC/MS analysis, we employed an Agilent 7890B GC combined with an Agilent 5977B MSD and a PAL 3 (RSI 85) chromatograph. The columns used were HP-5MS UI, 30 m × 0.25 mm with a film thickness of 0.25 μm, provided by Agilent Technologies, Inc. The analytical conditions were set with the column initially held at 35 °C for 5 min. Subsequently, the temperature was programmed to rise from 35 °C to 150 °C at a rate of 5 °C/min, then increasing by 15 °C/min to 250 °C, with a hold time of 90 min. The specific settings were as follows: Inlet temperature at 250 °C, detector



DOI: 10.5497/wjp.v12.i4.35

Figure 1 Yellow and green fruits harvested from the scrambling shrub *Capparis cartilaginea* contain a different set of components. A: Yellow fruit; B: Green fruit.

temperature at 280 °C, split injection ratio of 1:5, initial temperature at 100 °C, and initial time set to 4.0 min. Helium was used as the carrier gas with a flow rate of 1 mL/min.

For compound detection and identification, we referenced various standards, retention times, and retention indices (Table 1). Additionally, we consulted multiple libraries: NIST/EPA/NIH Mass Spectral Library 2017, Wiley Registry of Mass Spectral Data 11th Edition, FFNSC3, © 2015, and the Adams EO library, Mass Spectral Library, containing 2205 compounds. In total, 58 volatile compounds were detected, with 42 of them being positively identified. This identification was based on a comparison of their mass spectra and retention times, along with their Kovats retention indices, either to those of injected standards or by referencing the National Institute of Standards and Technology's Mass Spectral Library database.

Comparison of biological activities of natural isothiocyanates

The principle that the chemical structure of natural or synthetic molecules dictates their biological activity has been recognized for over 150 years and is referred to as structure-activity relationships (SAR). This concept was first introduced by Brown and Fraser[15] in 1868. However, according to alternate sources[16], the SAR notion was earlier employed in the realm of toxicology. In this context, Cros determined the correlation between the toxicity of primary aliphatic alcohols and their water solubility as early as 1863.

In this particular study, we sourced PASS predictions for approximately 28 isothiocyanates derived from various plants. These PASS estimates are represented as Pa values. Each Pa value signifies the likelihood of a compound being categorized under "actives" for a given predicted biological activity. A higher Pa value denotes greater confidence in the anticipated biological activity[17,18].

RESULTS

Various components from leaves, buds, stems, aerial parts, and seeds of different plant species within the *Capparis* genus have been documented in the literature. Yet, no literature data was found pertaining to the study of yellow and green fruits or jam derived from *C. cartilaginea*. Based on our GC/MS findings, the primary constituents of the yellow fruits were identified as 2-butyl isothiocyanate (49.43%) and isopropyl isothiocyanate (48.74%), as visualized in the chromatogram (Figure 2A). A similar compositional profile was observed for the green fruits, with the dominant components being 2-butyl isothiocyanate (49.76%) and isopropyl isothiocyanate (46.68%), as shown in Table 2 and illustrated in the chromatogram (Figures 2B and 3).

The GC/MS analysis of the seeds from *C. cartilaginea* revealed dimethylsulfide as the predominant component, constituting 55.82%, while the content of 2-butyl isothiocyanate was notably lower at just 6.8%. These findings can be referenced in Table 3 and visualized in the chromatogram (Figure 2C). Furthermore, the GC/MS analysis of jam derived from *C. cartilaginea* indicated that its primary components were hexanedioic acid bis(2-ethylhexyl) ester at 61.99%, limonene (covering both isomers) at 8.51%, dimethyl sulfide at 3.85%, 2-butyl isothiocyanate at 3.29%, dodecanoic acid 1-methylethyl ester at 2.16%, and pentanoic acid, 2-ethylhexyl ester at 2.01% (Figures 2D and Table 4). The molecular structures of these identified compounds are depicted in Figure 4. Tuvia Naor jam consists of the fruits of *C. cartilaginea* (or *Capparis inermis*, or a synonym for *Capparis sinaica*). Homemade jam Tuvia capparis Jam from the fruits of *C. cartilaginea* contains 36% fruit, sugar, apple, lemon, and flavors.

DISCUSSION

The experimental data reveals that all parts of plants from the *Capparis* genus contain isothiocyanates in varying concentrations. It was intriguing to discern which specific isothiocyanates were present in this genus. This curiosity stems from

Table 1 Composition of components that were identified from yellow fruits of *Capparis cartilaginea*

Peak	RT	Area	%	Compound	RI
1	2.477	67563.26	0.16	Isopropylnitrile	623
2	4.145	48903.53	0.11	N-methylene-ethenamine	727
3	8.089	20864469.13	48.74	Isopropyl isothiocyanate	837
4	10.846	55386.82	0.13	2-butenyl isothiocyanate	887
5	11.832	21159669.73	49.43	2-butyl isothiocyanate	920
6	12.578	597488.12	1.40	Isobutyl isothiocyanate	926
7	25.268	17767.47	0.04	Benzyl isothiocyanate	1359

RT: Retention time; RI: Retention index.

Table 2 Composition of components that were identified from green fruits of *Capparis cartilaginea*

Peak	RT	Area	%	Compound	RI
1	1.756	283022.83	0.19	Dimethylsulfide	520
2	2.453	308033.24	0.21	Isobutyronitrile	626
3	3.864	23282.6	0.02	Sec-butyl cyanate	689
4	4.145	284696.04	0.19	N-methylene-ethenamine	727
5	6.991	10973.58	0.01	Ethyl isothiocyanate	796
6	8.193	68423753.03	46.68	Isopropyl isothiocyanate	837
7	10.59	6355.8	0.00	Propyl isothiocyanate	881
8	10.854	393825.2	0.27	2-butenyl isothiocyanate	887
9	11.929	72938834.61	49.76	2-butyl isothiocyanate	920
10	12.586	3848951.24	2.63	Isobutyl isothiocyanate	926
11	25.276	70246.54	0.05	Benzyl isothiocyanate	1359

RT: Retention time; RI: Retention index.

Table 3 Composition of components that were identified from seeds of *Capparis cartilaginea*

Peak	RT	Area	%	Compound	RI
1	1.779	557486.8	55.82	Dimethylsulfide	520
2	2.493	18043.82	1.81	Isobutyronitrile	626
3	2.822	41394.08	4.14	3-methylbutanal	652
4	2.958	31612.69	3.17	2-methyl-butanal	662
5	8.112	280745.6	28.11	Isopropyl isothiocyanate	837
6	11.84	67963.7	6.80	2-butyl isothiocyanate	920
7	12.618	1561.57	0.16	Isobutyl isothiocyanate	926

RT: Retention time; RI: Retention index.

the fact that isothiocyanates are invaluable plant metabolites known for their broad spectrum of biological activities. Notably, certain isothiocyanates are incorporated into Tibetan and Chinese medicinal practices[19-21]. These naturally occurring molecules originate from glucosinolate precursors found in cruciferous vegetables[19,22-25].

Tables 5 and 6 provide a quantitative breakdown of the distribution of isothiocyanates across different plant species within the *Capparis* genus, collected from various global regions. While many articles discuss isothiocyanates, not all

Table 4 Composition of components that were identified from jam of *Capparis cartilaginea*

Peak	RT	Area	%	Compound	RI
1	1.788	272484.92	3.85	Dimethyl sulfide	520
2	2.453	59609.49	0.84	Isobutyronitrile	626
3	2.814	96185.08	1.36	3-methyl-butanal	652
4	2.926	34760.26	0.49	2-methyl-butanal	662
5	4.161	145138.02	2.05	N-methylene-ethenamine	727
6	8.113	85740.89	1.21	Isopropyl isothiocyanate	837
7	11.824	232997.63	3.29	2-butyl isothiocyanate	920
8	12.61	6608.49	0.09	Isobutyl isothiocyanate	926
9	13.347	77903.33	1.10	β-pinene	979
10	13.981	7385.93	0.10	β-myrcene	991
11	14.806	8950.21	0.13	α-terpinene	1018
12	15.079	5640.69	0.08	P-cymene	1025
13	15.215	601965.53	8.51	Limonene	1030
14	15.296	13202.57	0.19	Eucalyptol	1032
15	16.249	112624.11	1.59	γ-terpinene	1060
16	17.219	7218.34	0.10	Terpinolene	1088
17	20.402	11884.14	0.17	α-terpineol	1189
18	25.261	57235.71	0.81	2-(2-butoxyethoxy)-ethanol acetate	1366
19	26.638	142269.27	2.01	Pentanoic acid, 2-ethylhexyl ester	1404
20	28.014	76710.10	1.08	1-dodecanol	1473
21	28.59	25321.22	0.36	Pentadecane	1500
22	30.152	13471.82	0.19	Diphenyl sulfide	1552
23	30.264	83985.94	1.19	Hexadecane	1600
24	30.45	11616.10	0.16	Octadecanal	1357
25	30.636	152595.56	2.16	Dodecanoic acid 1-methylethyl ester	1618
26	31.408	80674.69	1.14	2-propenoic acid dodecyl ester	1675
27	31.473	41016.71	0.58	Heptadecane	1700
28	31.547	53606.2	0.76	(1-methyldecyl)-benzene	1708
29	31.64	73991.74	1.05	(1-methyldecyl)-benzene	1735
30	32.189	9636.895	0.14	2-methyl-octadecane	1863
31	32.449	27402.23	0.39	Nonadecane	1900
32	33.491	19861.16	0.28	Hexadecanoic acid methyl ester	1926
33	33.732	28833.81	0.41	Hexadecanoic acid	1968
34	34.021	9930.393	0.14	Heneicosane	2100
35	37.182	4384622	61.99	Hexanedioic acid bis(2-ethylhexyl) ester	2398

RT: Retention time; RI: Retention index.

provide specific percentages, hence we have refrained from citing such articles. The molecular structures of isothiocyanates extracted from various *Capparis* species are illustrated in Figure 5.

Isothiocyanates, which originate from glucosinolate precursors in cruciferous plants, are recognized as some of the most potent chemoprophylactic agents. Numerous studies affirm that both natural and synthetic isothiocyanates possess anticarcinogenic properties, as they not only diminish the activation of carcinogens but also augment their detoxification [44-48]. Moreover, they demonstrate antitumor capabilities, influencing a myriad of pathways such as apoptosis, MAPK

Table 5 Production of main isothiocyanates in essential oils of the genus *Capparis* collected in different world regions

Species, tissues	Collected place	1	2	4	5	6	7	8	12	13	17	Ref.
C. flexuosa, leaves	Brazil				11.2						79.3	[26]
C. spinosa, leaves and flower buds	Croatia	92.1			0.4		0.3					[11,27]
C. spinosa, leaves	Jordan	25.6		28.9								[28]
C. cartilaginea, leaves	Jordan	31.8	2.5	18.2		5.4						[28]
C. spinosa var. aegyptiaca	Egypt	24.7		12.4	3.2							[29]
C. cartilaginea, leaves	Egypt				65.0				29.9			[30]
C. deserti, leaves	Egypt				68.7				20.0			[30]
C. spinosa, fruits	Iran			13.7	10.6					15.6		[31]
C. cartilaginea, yellow fruits	Israel			48.7		1.4	49.4	0.1				This study
C. cartilaginea, green fruits	Israel		0.1	46.7		2.6	49.8	0.3				This study
C. cartilaginea, seeds	Israel			28.1		0.2	6.8					This study
C. cartilaginea, jam	Israel			1.2		0.1	3.3					This study
C. spinosa, leaves	Syria	25.6		28.9		16.6		2.2				[32]
C. ovata, buds	Turkey	4.5	1.5		0.1	0.2						[33]
C. ovata, leaves	Turkey	20.0	1.6		0.5	0.3						[33]
C. cartilaginea, leaves	Yemen			69.4	26.9	3.3						[34]

signaling, oxidative stress, and cell cycle progression[47-51].

The process through which natural isothiocyanates are formed *via* the hydrolysis of glucosinolates, facilitated by the enzyme β-thioglucosidase (known as myrosinase), is depicted in Figure 6. This biosynthetic mechanism is well-established, with isothiocyanates being identified in both plants and fungi[52-54]. Utilizing the PASS computer program, we computed the activity of natural isothiocyanates extracted from plants within the *Capparis* genus. The ensuing data is outlined in Table 7. As the table reveals, the primary properties pertaining to biological activity encompass apoptosis agonist, chemoprotective, chemosensitizer, and antineoplastic functions.

Benzyl isothiocyanate (9) has been extracted from *Capparis spinosa* (*C. spinosa*) components. Traditionally, fresh parts of this plant, particularly the flower buds, have been consumed as accompaniments to olives, cheese, and nuts. This plant stands out as one of the most cherished aromatic varieties native to the Mediterranean region. The fermentation of different parts of *C. spinosa* not only renders the capers consumable but also shapes their distinct taste, along with their organoleptic and nutritional attributes[54]. The biological activity of benzyl isothiocyanate is depicted in a 3D graph, as illustrated in Figures 7 and 8A.

Table 6 Production of main isothiocyanates in essential oils of the genus *Capparis* collected in different world regions

Species, tissues	Collected place	1	4	5	6	Ref.
C. decidua, leaf	Pakistan		11.0	6.3		[34]
C. spinosa, leaves	Spain	87.2		0.1	0.8	[35]
C. spinosa, stems	Spain	86.6		0.1	0.4	[35]
C. spinosa, flower buds	Spain	65.3				[35]
C. spinosa, aerial parts	Saudi Arabia	31.6		1.1		[36]
C. cartilaginea, leaves	Kenya	31.8			3.2	[37]

Advanced ovarian cancer cannot be cured by surgery alone; chemotherapy is vital for its treatment. While isothiocyanates have been shown to inhibit carcinogen-induced tumorigenesis in animal models, their therapeutic potential in advanced ovarian cancer remains unexplored. Kalkunte *et al*[55] demonstrated that benzyl isothiocyanate, commonly found in cruciferous vegetables like broccoli, cabbage, and watercress, suppresses the proliferation of advanced ovarian cancer cells and triggers apoptosis. Preliminary studies indicate its potential in both preventing and treating various cancers. Given this evidence, more research is essential to confirm its efficacy in humans and to advance its potential as a prophylactic or therapeutic agent, maximizing therapeutic outcomes while minimizing toxicity in cancer treatments[47].

In our study, we examined the volatile components of yellow and green fruits from the scrambling shrub *C. cartilaginea* . Additionally, we delved into the composition of seeds and jam derived from *C. cartilaginea* using GC/MS analysis. We detected isothiocyanates in all plant samples studied. This research presents a comprehensive overview of isothiocyanates identified in the *Capparis* genus, gathered from various global regions. Through the PASS program, we ascertained the biological activities of these isothiocyanates. Our findings revealed that these compounds are promising apoptosis agonists with potential as potent antitumor agents. Furthermore, we identified additional biological activities. The insights provided in this study hold substantial practical relevance and could pave the way for medical applications. The term "chemoprotective" refers to the properties of a substance that helps protect cells and tissues from the toxic effects of chemicals or against the DNA damage that can lead to cancer. In other words, chemoprotective agents help prevent or reduce the risk of chemically induced diseases, including various forms of cancer. Chemoprotective properties can arise from a variety of mechanisms: (1) Antioxidant activity: Many chemoprotective agents can neutralize free radicals, reducing oxidative stress, which can cause DNA damage and potentially lead to cancer; (2) Detoxification: Certain substances can enhance the body's detoxification processes, helping to remove or neutralize potential carcinogens before they can cause harm; (3) Enhancement of DNA repair: Some agents can boost the mechanisms that repair damaged DNA; (4) Inhibition of carcinogen activation: Some chemicals need to be activated in the body to become carcinogenic. Chemoprotective agents can inhibit the enzymes responsible for this activation; (5) Suppression of carcinogen binding to DNA: By preventing carcinogens from binding to DNA, chemoprotective agents can reduce the risk of mutations that might lead to cancer; and (6) Inhibition of tumor growth: Some agents can slow or stop the growth of tumors by affecting cell cycle progression, inducing apoptosis (programmed cell death) or suppressing the blood supply to tumors (anti-angiogenesis).

Natural foods, especially fruits, vegetables, and spices, are rich sources of chemoprotective compounds. Examples include the isothiocyanates from cruciferous vegetables, polyphenols from green tea, curcumin from turmeric, and resveratrol from grapes, among many others. In the context of cancer, chemoprotection can also refer to strategies or agents used to protect normal tissues from the harmful side effects of chemotherapy while allowing the drugs to act on cancer cells.

Ethyl-(2), allyl-(14), and 3-methyl-3-butenyl-isothiocyanates (17) exhibited a pronounced apoptosis agonist activity, with confidence levels exceeding 95%. The associated 3D graph (Figure 8B) visually represents their activities. Another visual representation can be observed in Figure 8C, where three specific isothiocyanates stand out due to their robust anti-*Helicobacter pylori* activity, which exhibits over 80% confidence. Among these, anticancer properties are the most prominent.

Furthermore, isothiocyanates labeled as 26, 27, and 28 provide compelling data, as illustrated in Figure 8D. Not only do these compounds demonstrate potent apoptosis agonist activity, surpassing 93% confidence, but they also show promise in treating periodontitis with a confidence level exceeding 70%.

"Anti-*Helicobacter pylori* activity" refers to the ability of a substance to inhibit or eradicate *Helicobacter pylori* bacteria. *Helicobacter pylori* is a type of bacteria that can infect the stomach and is known to be a main cause of peptic ulcers, and its persistent infection has also been linked to stomach cancer. Therefore, substances with anti-*Helicobacter pylori* activity may help in preventing or treating these conditions.

Substances with anti-*Helicobacter pylori* activity might function through various mechanisms, such as: (1) Inhibiting the growth or reproduction of the bacteria; (2) Killing the bacteria directly; and (3) Disrupting the mechanisms by which the bacteria cause disease (for instance, by neutralizing toxins produced by the bacteria).

Anti-*Helicobacter pylori* activity can be exhibited by antibiotics, as well as various other natural and synthetic compounds, and is an area of interest in pharmacology and medicinal chemistry due to the importance of managing infections by this bacterium. Research into substances with anti-*Helicobacter pylori* activity may yield new treatments for infections and possibly for preventing stomach ulcers and cancer.

Table 7 Predicted biological activity of isothiocyanates derived from essential oils of the genus *Capparis*

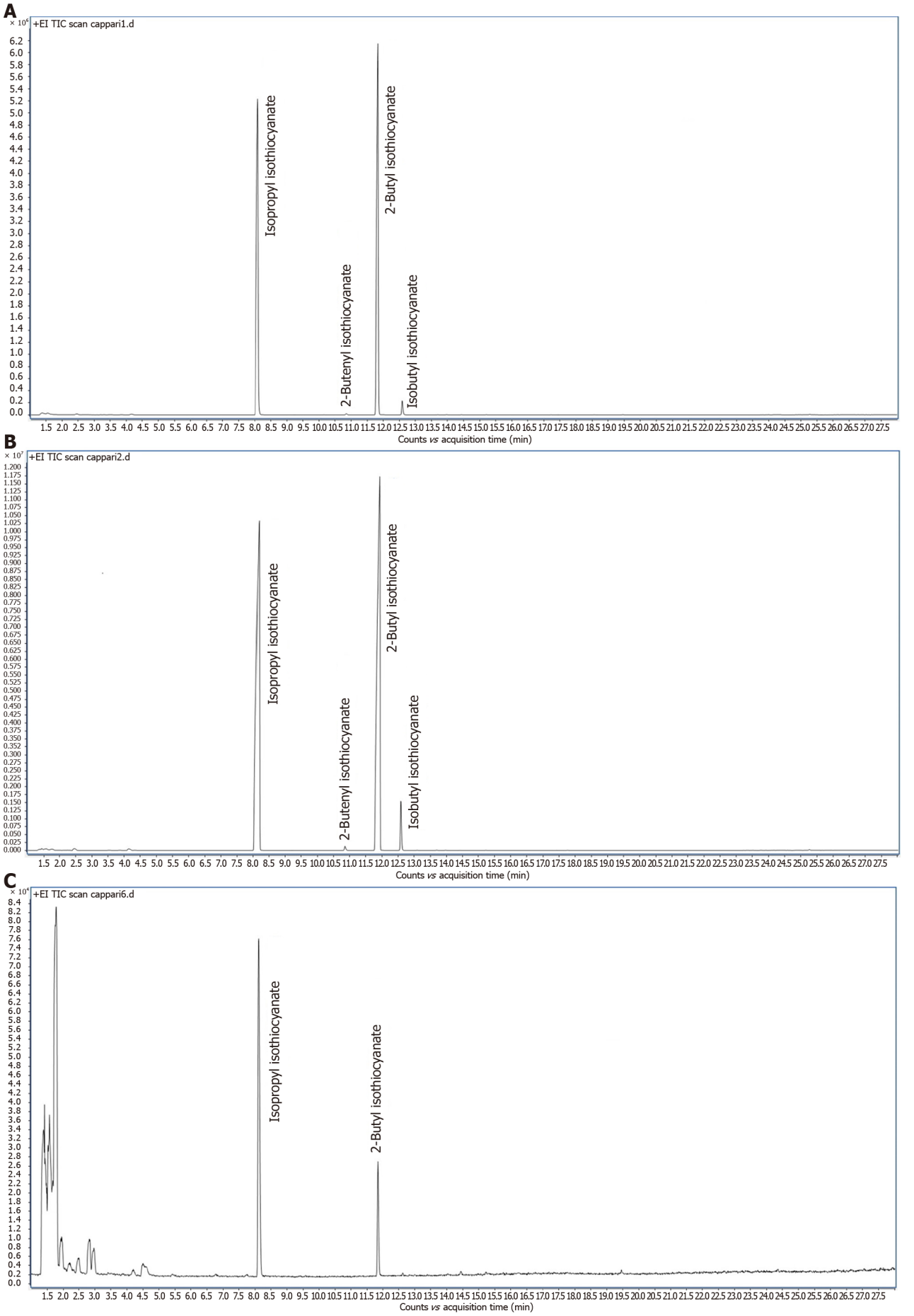
No	Anticancer properties. Pa[1]	Anti-infectives properties. Pa[1]
1	Apoptosis agonist (0.963)	Anti-schistosomal (0.759)
	Chemoprotective (0.871)	Antiviral (arbovirus) (0.638)
	Antineoplastic (0.794)	Anti-seborrheic (0.614)
2	Apoptosis agonist (0.965)	Anti-*Helicobacter pylori* (0.853)
	Chemoprotective (0.890)	Anti-seborrheic (0.749)
	Chemosensitizer (0.798)	Anti-schistosomal (0.711)
	Antineoplastic (0.789)	Antiparasitic (0.537)
3	Apoptosis agonist (0.956)	Anti-*Helicobacter pylori* (0.816)
	Chemoprotective (0.866)	Anti-seborrheic (0.690)
	Chemosensitizer (0.779)	Antiviral (arbovirus) (0.635)
	Antineoplastic (0.743)	Anti-schistosomal (0.612)
4	Apoptosis agonist (0.914)	Anti-*Helicobacter pylori* (0.720)
	Chemoprotective (0.819)	Anti-schistosomal (0.687)
	Chemosensitizer (0.726)	Anti-seborrheic (0.684)
5	Apoptosis agonist (0.956)	Anti-*Helicobacter pylori* (0.816)
	Chemoprotective (0.858)	Antiviral (arbovirus) (0.690)
	Chemosensitizer (0.778)	Anti-schistosomal (0.594)
	Antineoplastic (0.751)	Antiparasitic (0.570)
6	Apoptosis agonist (0.951)	Anti-*Helicobacter pylori* (0.804)
	Chemoprotective (0.850)	Anti-seborrheic (0.731)
	Chemosensitizer (0.765)	Anti-schistosomal (0.665)
	Antineoplastic (0.720)	Antiparasitic (0.524)
7	Apoptosis agonist (0.867)	Antiviral (arbovirus) (0.654)
	Chemoprotective (0.782)	Anti-seborrheic (0.650)
	Chemosensitizer (0.694)	Anti-*Helicobacter pylori* (0.624)
8	Apoptosis agonist (0.955)	Anti-*Helicobacter pylori* (0.822)
	Chemoprotective (0.839)	Antiparasitic (0.680)
	Antineoplastic (0.833)	Anti-helmintic (0.632)
	Chemosensitizer (0.791)	Antifungal (0.568)
9	Apoptosis agonist (0.965)	Anti-*Helicobacter pylori* (0.629)
	Antineoplastic (0.825)	Anti-schistosomal (0.598)
	Chemoprotective (0.782)	
	Chemosensitizer (0.696)	
10	Apoptosis agonist (0.933)	Anti-*Helicobacter pylori* (0.739)
	Chemoprotective (0.847)	
	Antineoplastic (0.728)	
	Chemosensitizer (0.722)	
11	Apoptosis agonist (0.884)	Anti-*Helicobacter pylori* (0.679)
	Chemoprotective (0.812)	
	Antineoplastic (0.714)	
	Chemosensitizer (0.661)	

12	Apoptosis agonist (0.956)	Anti-*Helicobacter pylori* (0.703)
	Chemoprotective (0.825)	
	Chemosensitizer (0.741)	
	Antineoplastic (0.740)	
	Antineoplastic (genitourinary cancer) (0.581)	
13	Apoptosis agonist (0.856)	Anti-*Helicobacter pylori* (0.703)
	Chemoprotective (0.825)	
	Chemosensitizer (0.741)	
	Antineoplastic (0.740)	
	Antineoplastic (genitourinary cancer) (0.581)	
14	Apoptosis agonist (0.959)	Anti-*Helicobacter pylori* (0.792)
	Chemoprotective (0.867)	Antiparasitic (0.609)
	Chemosensitizer (0.787)	Anti-helmintic (0.581)
	Antineoplastic (0.775)	Antis-chistosomal (0.574)
15	Apoptosis agonist (0.923)	Anti-*Helicobacter pylori* (0.659)
	Chemoprotective (0.817)	Antifungal (0.658)
	Antineoplastic (0.771)	Antiparasitic (0.560)
	Chemosensitizer (0.728)	
16	Apoptosis agonist (0.919)	Anti-*Helicobacter pylori* (0.752)
	Chemoprotective (0.821)	Antiviral (arbovirus) (0.730)
	Antineoplastic (0.751)	Antifungal (0.678)
	Chemosensitizer (0.747)	Antiparasitic (0.672)
17	Apoptosis agonist (0.953)	Anti-*Helicobacter pylori* (0.753)
	Chemoprotective (0.830)	Antifungal (0.533)
	Antineoplastic (0.781)	
	Chemosensitizer (0.754)	
18	Antineoplastic (myeloid leukemia) (0.805)	Anti-eczematic (0.606)
	Chemosensitizer (0.742)	
19	Apoptosis agonist (0.952)	Anti-*Helicobacter pylori* (0.769)
	Chemoprotective (0.847)	Anti-eczematic (0.610)
	Chemosensitizer (0.764)	Antifungal (0.575)
	Antineoplastic (0.753)	Anti-schistosomal (0.502)
20	Apoptosis agonist (0.955)	Anti-*Helicobacter pylori* (0.901)
	Chemoprotective (0.911)	Anti-ulcerative (0.611)
	Antineoplastic (0.781)	
	Chemosensitizer (0.694)	
	Anticarcinogenic (0.573)	
	Chemopreventive (0.559)	
21	Apoptosis agonist (0.851)	Anti-*Helicobacter pylori* (0.691)
	Chemoprotective (0.839)	
	Chemosensitizer (0.747)	
	Antineoplastic (0.733)	
	Antineoplastic (genitourinary cancer) (0.627)	

22	Apoptosis agonist (0.951)	Anti-seborrheic (0.775)
	Antineoplastic (0.820)	Antifungal (0.543)
	Chemoprotective (0.752)	Anti-*Helicobacter pylori* (0.542)
	Chemosensitizer (0.673)	
	Preneoplastic conditions treatment (0.559)	
23	Apoptosis agonist (0.929)	Anti-*Helicobacter pylori* (0.780)
	Chemoprotective (0.832)	Antiviral (arbovirus) (0.626)
	Chemosensitizer (0.771)	Antiparasitic (0.589)
	Antineoplastic (0.762)	Anti-helmintic (0.559)
	Preneoplastic conditions treatment (0.515)	
24	Apoptosis agonist (0.932)	Anti-*Helicobacter pylori* (0.736)
	Chemoprotective (0.819)	Anti-schistosomal (0.579)
	Chemosensitizer (0.742)	Antifungal (0.550)
	Antineoplastic (0.675)	Antiviral (arbovirus) (0.531)
	Preneoplastic conditions treatment (0.541)	Antiparasitic (0.529)
25	Apoptosis agonist (0.930)	Anti-*Helicobacter pylori* (0.715)
	Chemoprotective (0.828)	Antiviral (arbovirus) (0.639)
	Antineoplastic (0.792)	Antifungal (0.620)
	Chemosensitizer (0.754)	
26	Apoptosis agonist (0.938)	Periodontitis treatment (0.752)
	Chemoprotective (0.827)	Anti-*Helicobacter pylori* (0.739)
	Antineoplastic (0.740)	Antifungal (0.622)
	Chemosensitizer (0.736)	Antiviral (arbovirus) (0.599)
	Preneoplastic conditions treatment (0.593)	
27	Apoptosis agonist (0.937)	Periodontitis treatment (0.727)
	Chemoprotective (0.820)	Anti-*Helicobacter pylori* (0.718)
	Antineoplastic (0.742)	Antifungal (0.644)
	Chemosensitizer (0.728)	Antiviral (arbovirus) (0.563)
	Preneoplastic conditions treatment (0.563)	
28	Apoptosis agonist (0.934)	Periodontitis treatment (0.751)
	Chemoprotective (0.823)	Anti-*Helicobacter pylori* (0.733)
	Antineoplastic (0.740)	Antifungal (0.639)
	Chemosensitizer (0.732)	Antiviral (arbovirus) (0.621)
	Preneoplastic conditions treatment (0.613)	

[1]Only activities with Pa > 0.5 are shown.

Periodontitis refers to a serious gum infection that damages the soft tissue and destroys the bone that supports your teeth. It can lead to tooth loss or worse, if not treated. Periodontitis is common but largely preventable. It is usually the result of poor oral hygiene. Key points about periodontitis include: (1) Cause: It is primarily caused by bacteria that adhere to and grow on the tooth's surfaces, along with an aggressive immune response against these bacteria; (2) Symptoms: Red or swollen gums, tender or bleeding gums, painful chewing, loose teeth, sensitive teeth, bad breath that does not go away, and receding gums or longer appearing teeth; (3) Risk factors: Periodontitis can be influenced by several factors including poor oral hygiene, tobacco use, diabetes, age, genetics, certain medications, and other conditions like decreased immunity; (4) Complications: If left untreated, periodontitis can result in tooth loss. It can also increase the risk of stroke, heart attack, and other health problems; and (5) Treatment: Treatment usually involves good dental hygiene practices, scaling, and root planning (deep cleaning) to remove the plaque and tartar, and in more severe cases, surgical treatments. Regular dental checkups and good oral hygiene can help prevent periodontal disease.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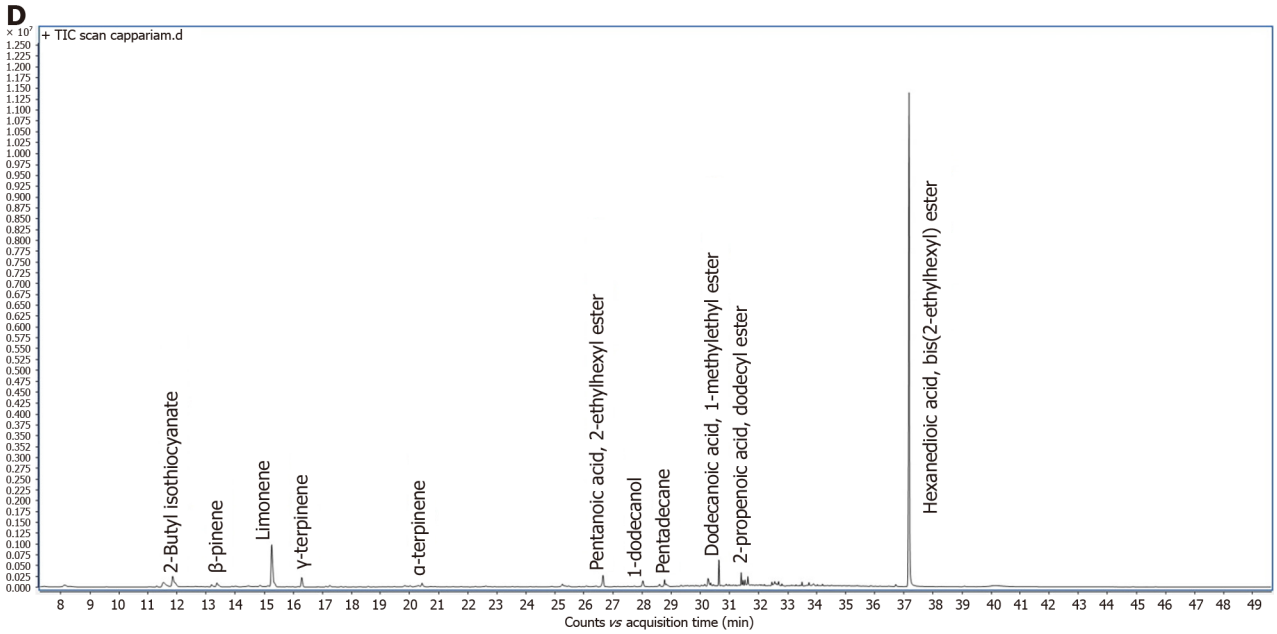

DOI: 10.5497/wjp.v12.i4.35

Figure 2 Gas chromatography-mass spectrometry chromatogram of compounds which were identified from yellow and green fruits, seeds, and jam of *Capparis cartilaginea*. A: Yellow fruits; B: Green fruits; C: Seeds; D: Jam.

DOI: 10.5497/wjp.v12.i4.35

Figure 3 Seeds of the scrambling shrub *Capparis cartilaginea*.

CONCLUSION

In our study, we examined the volatile components of yellow and green fruits from the scrambling shrub *C. cartilaginea*. Additionally, we delved into the composition of seeds and jam derived from *C. cartilaginea* using GC/MS analysis. We detected isothiocyanates in all plant samples studied. This research presents a comprehensive overview of isothiocyanates identified in the *Capparis* genus, gathered from various global regions. Through the PASS program, we ascertained the biological activities of these isothiocyanates. Our findings revealed that these compounds are promising apoptosis agonists with potential as potent antitumor agents. Furthermore, we identified additional biological activities. The insights provided in this study hold substantial practical relevance and could pave the way for medical applications.

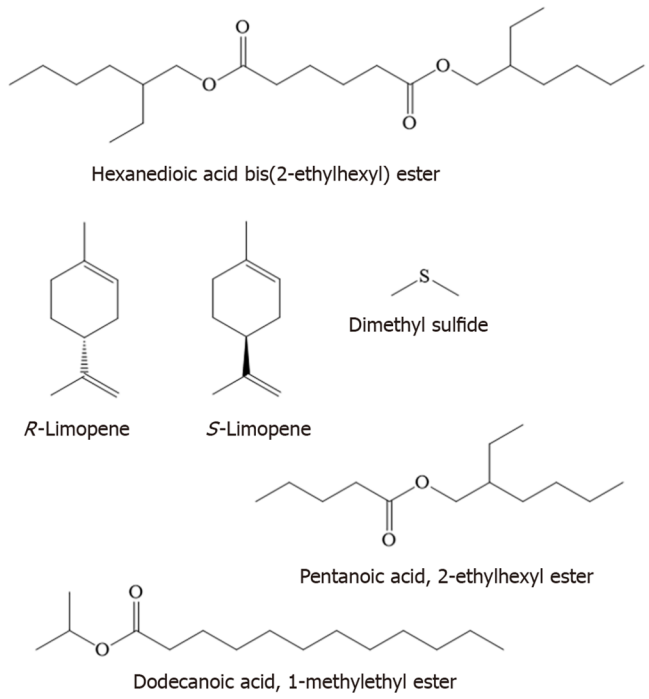

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Figure 4 Major metabolites that have been identified in *Capparis cartilaginea* jam.

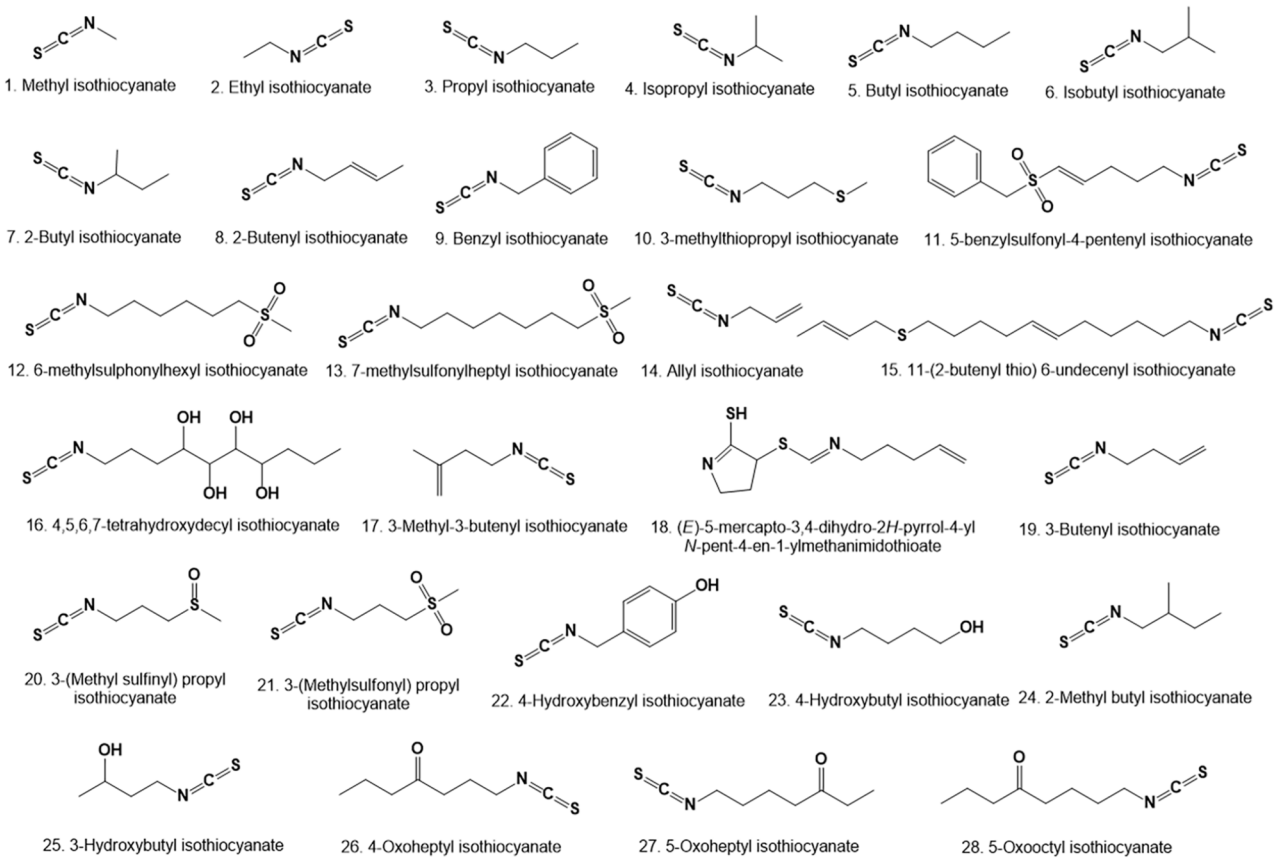

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Figure 5 Isothiocyanates found in plant extracts of the genus *Capparis*. These compounds were identified by gas chromatography-mass spectrometry and other physical-chemical methods[26-43].

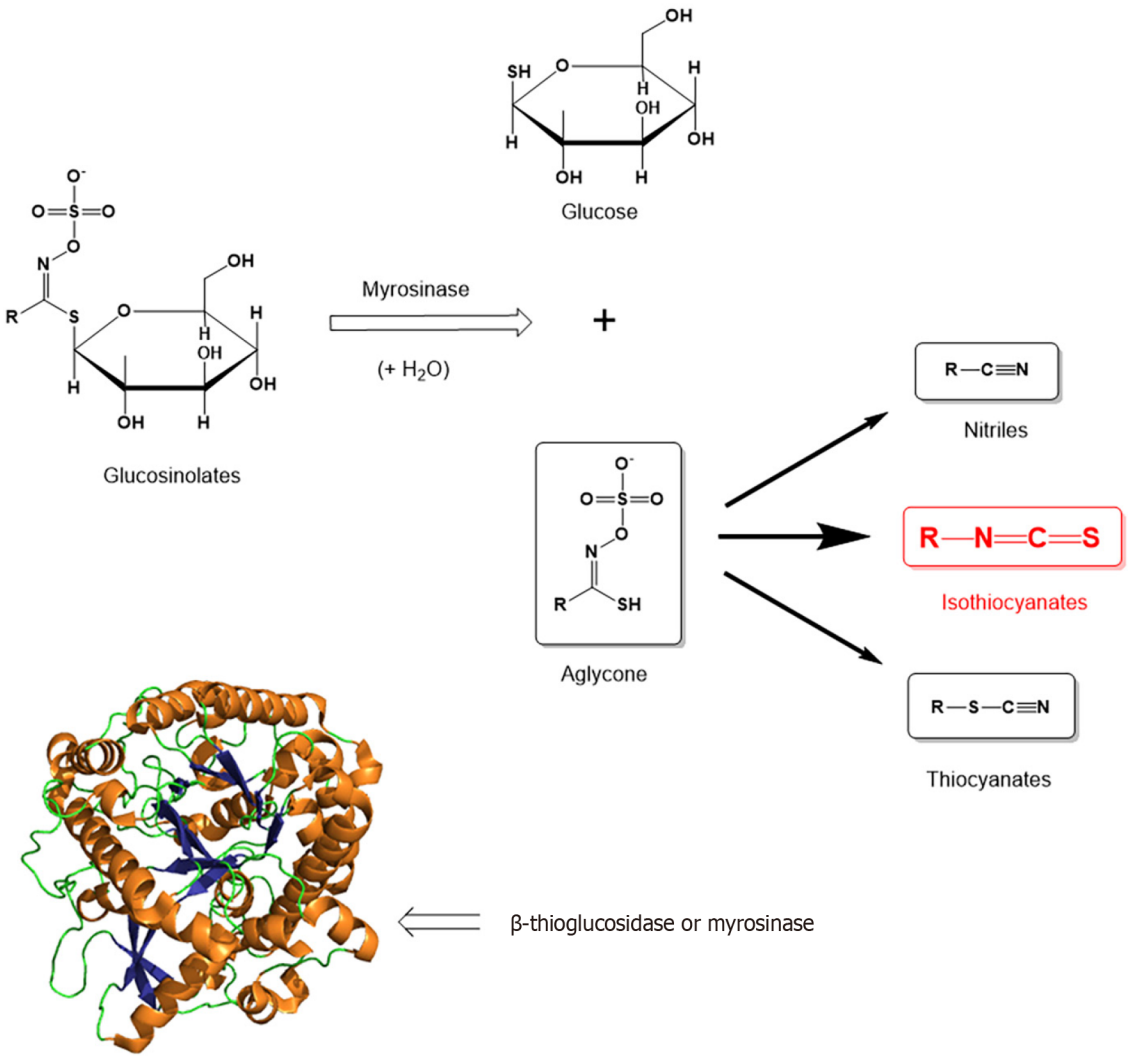

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Figure 6 Myrosinase (or β-thioglucosidase) which catalyzes the hydrolysis of glucosinolates to isothiocyanates, thiocyanates, nitriles, and other metabolites.

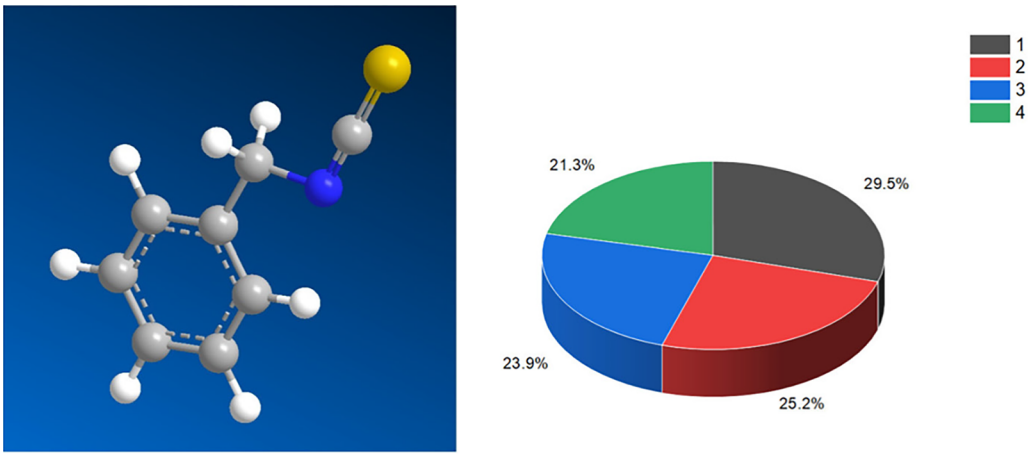

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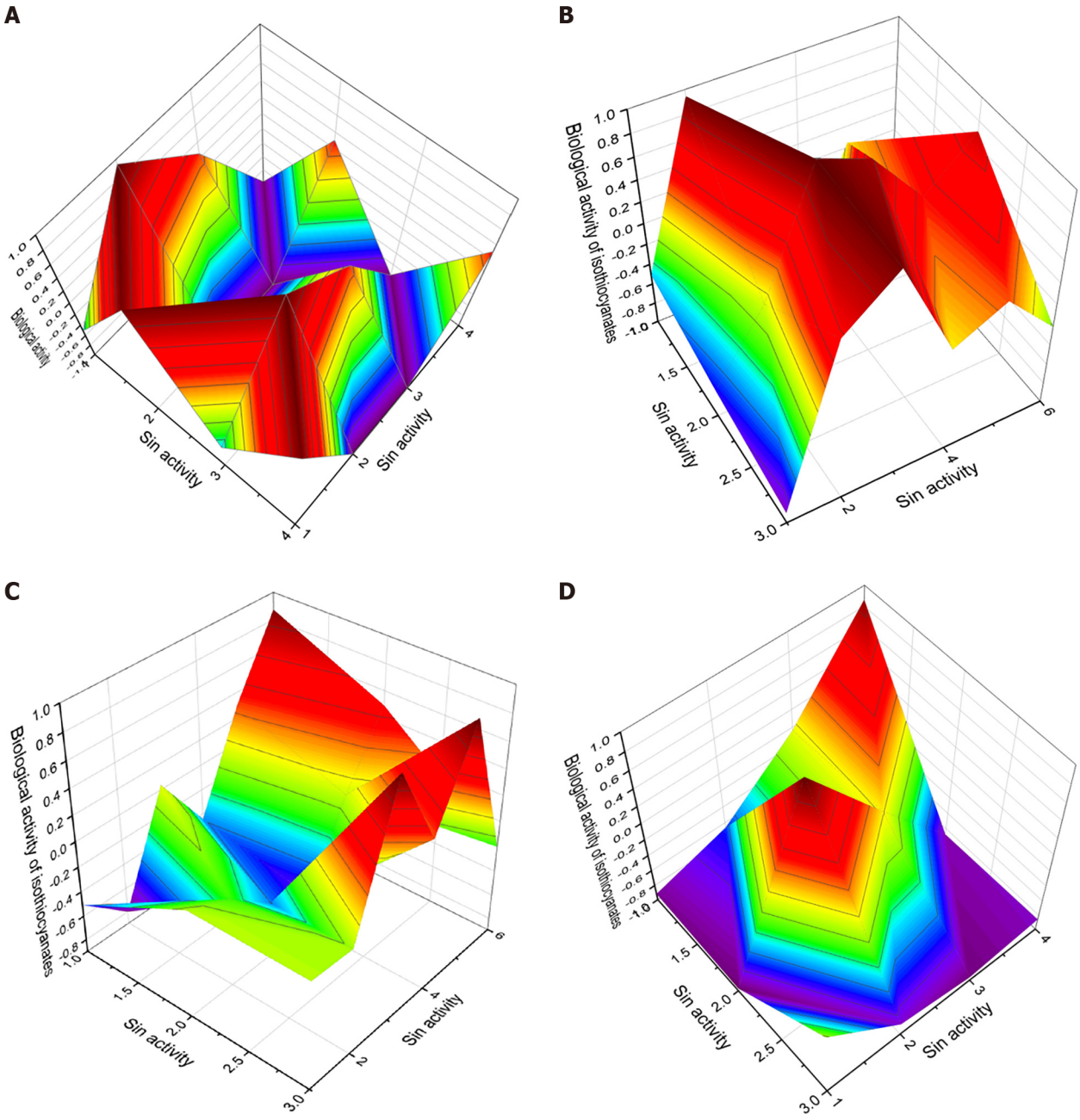
Figure 7 3D model (left) and percentage distribution of the dominant biological activity on the example benzyl isothiocyanate (9), which has a wide range of anticancer properties. Where activities are indicated under the numbers: (1) Apoptosis agonist (29.5%); (2) Antineoplastic (25%); (3) Chemoprotective (23.9%); and (4) Chemosensitizer (21.3%). The nitrogen atom is highlighted in blue, and sulfur atom is highlighted in brown.



DOI: 10.5497/wjp.v12.i4.35

Figure 8 3D graphs. A: 3D graph shows a wide range of biological activities and predicted pharmacological activities of benzyl isothiocyanate (9). This compound is characterized as an agonist of apoptosis. In addition, it exhibits antitumor properties and is an inhibitor of the development of the Gram-negative microaerophilic helical bacterium *Helicobacter pylori* (*H. pylori*). The *H. pylori* infection is known to be an important public health problem worldwide, with a prevalence of 45% to 84%. The *H. pylori* bacteria enter the digestive tract and can cause ulcers in the lining of the stomach or in the upper part of the small intestine, and patients can develop chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, stomach cancer, or peptic ulcer disease. Amoxicillin is commonly used to treat this infection, and it appears that isothiocyanates may be a potential drug for *H. pylori* infection; B: 3D graph shows the predicted and calculated biological activity of isothiocyanates (compound numbers: 2, 14, and 17) showing the highest degree of confidence. All presented natural isothiocyanates have a dominant activity as an apoptosis agonist with a confidence of more than 96%. The second activity that characterizes these isothiocyanates is chemoprotective; C: 3D graph shows the predicted and calculated anti-*H. pylori* activity of isothiocyanates (compound numbers: 5, 8, and 20) showing the highest degree of confidence, more than 82.2%; D: 3D graph shows the predicted and calculated activity of isothiocyanates against periodontitis (compound numbers: 26, 27, and 28) showing the highest degree of confidence, more than 73%.

ARTICLE HIGHLIGHTS

Research background

In the realm of medicinal chemistry, isothiocyanates are characterized by the -N=C=S functional group, which results from substituting the oxygen atom in the isocyanate group with sulfur. These compounds are predominantly found in plants and arise from the enzymatic conversion of metabolites, specifically glucosinolates. Notably, numerous plant-derived isothiocyanates have demonstrated anticarcinogenic properties. Their mechanism of action involves inhibiting

the activation of carcinogens and bolstering their detoxification processes.

Research motivation
Our motivation to undertake this study stemmed from the noticeable lack of extensive literature regarding isothiocyanates in food sources. While some health research has touched upon the use of isothiocyanates, comprehensive investigations into their potential benefits remain limited. Consequently, we embarked on an in-depth *in silico* study of isothiocyanates to assess their preliminary therapeutic properties.

Research objectives
To investigate the composition of fruits, seeds, and jam derived from the scrambling shrub *Capparis cartilaginea* (*C. cartilaginea*) utilizing gas chromatography-mass spectrometry (GC-MS) analysis, and to conduct an *in silico* examination of the biological activity associated with the isolated isothiocyanates.

Research methods
For our investigation, we employed the following methods: GC/MS analysis: This technique allowed us to accurately identify and quantify the volatile components present in the samples from the scrambling shrub *C. cartilaginea*; PASS computer program: We utilized the PASS software, which boasts a comprehensive database of over one million natural and synthetic compounds, paired with more than 10000 documented biological activities. As per data from its official website, this German-developed program is a popular tool among the scientific community, with over 26000 researchers from 34 different countries using it on an annual basis.

Research results
Our investigation revealed that isothiocyanates exhibit a significant anticancer potential. Additionally, these compounds display other potential biological activities, including antiviral, antibacterial, and antifungal properties.

Research conclusions
The findings from our investigation are promising. We identified the presence of isothiocyanates in jams, seeds, and fruits, which demonstrated potential anti-cancer properties. Nevertheless, further *in vitro* and *in vivo* studies are essential to validate these preliminary results.

Research perspectives
Moving forward, the intention is to conduct more in-depth GC/MS and PASS *in silico* analyses on individual isothiocyanates extracted from jams, seeds, and fruits of the Capparis genus. This will provide a clearer understanding of the properties and potential therapeutic applications of these compounds.

FOOTNOTES

Co-corresponding authors: Lumír Hanuš and Valery M Dembitsky.

Author contributions: Hanuš L carried out the extraction and analysis of volatile components of yellow and green fruits, seeds, and jam from the scrambling shrub *Capparis cartilaginea*; Naor T grew the material and provided it for analysis; Gloriozova T determined the biological activity of volatile components; Dembitsky VM prepared the article for publication and also wrote and reviewed this article; and all authors read and approved the final version of the manuscript. In addition, the co-corresponding authors contributed equally to the accompanying manuscript, such as describing the methods, their application to the analysis, and writing the discussion.

Institutional review board statement: The study was conducted *in silico* and did not include humans or animals, so a statement from the Institutional Review Board was not necessary.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The study was conducted only in a computational environment and the data and three-dimensional structures used are available in public online databases.

Country/Territory of origin: Israel

ORCID number: Lumir Hanus 0000-0003-0521-9928; Valery M Dembitsky 0000-0002-4603-8704.

S-Editor: Wang JJ
L-Editor: Wang TQ

P-Editor: Yu HG

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