

October 2022 Volume 36 Issue 10 ISSN 0951-418X

# Phytotherapy Research

An International Journal devoted to clinical and pharmacological evaluation  
of herbal medicines, nutraceuticals and natural product derivatives

View this journal online at [wileyonlinelibrary.com/journal/ptr](http://wileyonlinelibrary.com/journal/ptr)



WILEY

# Phytotherapy Research

## EDITOR-IN-CHIEF

Professor Angelo A. Izzo,  
University of Naples, Italy  
Email: [aaizzo@unina.it](mailto:aaizzo@unina.it)

## SENIOR EDITORS

Professor Sung-Hoon Kim,  
Kyunghee University, South Korea  
Email: [sungkim7@khu.ac.kr](mailto:sungkim7@khu.ac.kr)

Professor Rajan Radhakrishnan,  
Mohammed bin Rashid University, Dubai College of Medicine, UAE  
Email: [rajan.radhakrishnan@mbru.ac.ae](mailto:rajan.radhakrishnan@mbru.ac.ae)

## REVIEWS EDITOR

Dr Francesca Borrelli,  
University of Naples, Italy  
Email: [franborr@unina.it](mailto:franborr@unina.it)

## MANAGING EDITOR

Rachael Coveney  
E-mail: [phytotherapy.research@wiley.co.uk](mailto:phytotherapy.research@wiley.co.uk)

## FORMER EDITOR-IN-CHIEF

Professor Liz Williamson,  
University of Reading, UK  
Email: [e.m.williamson@reading.ac.uk](mailto:e.m.williamson@reading.ac.uk)

**Aims and Scope:** *Phytotherapy Research* is a monthly, international journal for the publication of original research papers, short communications, reviews and letters on medicinal plant research. Key areas of interest are pharmacology, toxicology, and the clinical applications of herbs and natural products in medicine, from case histories to full clinical trials, including studies of herb-drug interactions and other aspects of the safety of herbal medicines. Papers concerned with the effects of common food ingredients and standardised plant extracts, including commercial products, are particularly welcome, as are mechanistic studies on isolated natural products. Short communications dealing with the pharmacology and screening of crude or uncharacterised extracts will be considered for publication only if they are clearly of interest to our international readership and are not deemed more suitable for a regional audience. *Phytotherapy Research* does not publish agricultural, phytochemical, structure elucidation, quality control or botanical identification papers unless directly pertinent to the pharmacological effects or overall safety of plant based medicines currently in use.

## EDITORIAL BOARD

C. Anesini  
IQUIMEFA-CONICET, Pharmacology, Buenos Aires, Argentina

R. Arroo  
Leicester School of Pharmacy - Natural Products Research,  
De Montfort University, Leicester, UK

K. Asres  
Addis Ababa University, Ethiopia

J. Barnes  
University of Auckland, New Zealand

M. Botelho  
University of Potiguar, Brazil

K. J. Broadley  
Cardiff University, UK

F. Bucar  
University of Graz, Austria

V. Butterweck,  
Department of Pharmaceutics, University of Florida, USA

A. Capasso  
Universita degli Studi di Salerno, Italy

N. Chaiyakunapruk  
Monah University Malaysia, Malaysia

K.L. Chan  
University of Sains Malaysia, Penang, Malaysia

C.T. Che  
Department of Medicinal Chemistry & Pharmacognosy,  
University of Illinois at Chicago, USA

D. Curro  
University of Sains Malaysia, Penang, Malaysia

C-T. Che  
Department of Medicinal Chemistry & Pharmacognosy,  
University of Illinois at Chicago, USA

D. Curro  
Catholic University of the Sacred Heart, Rome, Italy

G. Esposito  
University of Rome "La Sapienza", Italy

S. Gibbons  
University of London, UK

A.H. Gilani  
Aga Khan University Medical College, Karachi, Pakistan

B. Hazra  
Jadavpur University, Calcutta, India

H. Hu  
China Agricultural University, Beijing, China

A.D. Kinghorn  
The Ohio State University, Columbus, OH, USA

L. Krenn  
University of Vienna, Austria

M.Lane  
University of London, UK

L. Lopes  
University of Sorocaba, Sao Paulo, Brazil

NN. Mimica-Dukic  
University of Novi Sad, Serbia

E. Pagano  
University of Naples, Italy

J.M. Pezzuto  
Long Island University, Brooklyn, USA

A. Sahebkar  
Mashhad University of Medical Sciences, Iran

J. Sarris  
Western Sydney University, Australia

A. Scholey  
Swinburne University, Melbourne, Australia

M. Simmonds  
Royal Botanical Gardens, Kew, UK

S. Srivastava  
Texas Tech University, USA

C. Wright  
University of Bradford, UK

## HONORARY EDITORIAL BOARD

F. Capasso  
University of Naples, Italy

E. A. Carlini  
Universidade Federal de São Paulo, Brazil

D.T. Okpako  
University of Ibadan, Nigeria

R.D.E. Sewell  
University of Wales, Cardiff, UK

R.C. Srimal  
Indian Institute of Toxicology Research,  
Lucknow, India

H. Wagner  
Ludwig-Maximilian University of Munich, Germany

P.G. Xiao  
Chinese Academy of Medical Sciences, Beijing, China

# Phytotherapy Research

PHYREH 36(10) 3673–4013 (2022)  
ISSN 0951-418X

VOLUME 36 NUMBER 10

October 2022

## Contents

### Letters to the Editor

- The commercial importance to develop validated analytical methods to define phytochemical levels in herbal medicinal products**  
I. DINI 3675
- Herbal adaptogens: An integrative approach for enhancing performance and resilience in athletes**  
S. RATHORE, B. K. KHUNTIA, M. WADHAWAN, V. SHARMA AND G. SHARMA 3678

### Reviews

- Pharmacology of  $\alpha$ -spinasterol, a phytosterol with nutraceutical values: A review**  
M. MAJEED, F. AHMAD, L. MUNDKUR AND S. APPIAN 3681
- Medicinal herbs in treating chemotherapy-induced nausea and vomiting: A review**  
R. RAJABALIZADEH, M. G. RAHBARDAR AND H. HOSSEINZADEH 3691
- The role of selected nutraceuticals in management of prediabetes and diabetes: An updated review of the literature**  
G. DEROSA, A. D'ANGELO AND P. MAFFIOLI 3709
- The effect of flaxseed oil consumption on blood pressure among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized clinical trials**  
T. MAHMUDIONO, S. A. JASIM, Y. S. KARIM, D. O. BOKOV, W. K. ABDELBASSET, K. S. AKHMEDOV, G. YASIN, L. THANGAVELU, Y. F. MUSTAFA, S. SHOUKAT, M. A. A. NAJM AND M. AMRAEI 3766
- The construction of preclinical evidence for the treatment of liver fibrosis with quercetin: A systematic review and meta-analysis**  
X. GUO, Y. LI, W. WANG, L. WANG, S. HU, X. XIAO, C. HU, Y. DAI, Y. ZHANG, Z. LI, J. LI, X. MA AND J. ZENG 3774
- The effect of flaxseed intake on appetite reduction: A systematic review of randomized clinical trials**  
M. ZAREI, S. ADELI, S. HOSSEINI AND E. DANESHZAD 3792
- Xanthotoxin (8-methoxypsoralen): A review of its chemistry, pharmacology, pharmacokinetics, and toxicity**  
A. WU, J. LU, G. ZHONG, L. LU, Y. QU AND C. ZHANG 3805
- Promising natural products against SARS-CoV-2: Structure, function, and clinical trials**  
Y. ZHAO, S. DENG, Y. BAI, J. GUO, G. KAI, X. HUANG AND X. JIA 3833
- Crocin molecular signaling pathways at a glance: A comprehensive review**  
M. BOOZARI AND H. HOSSEINZADEH 3859

### Research Articles

- Potato protease inhibitor II prevents obesity by inducing browning of white adipose tissue in mice via  $\beta_3$  adrenergic receptor signaling pathway**  
N. ZHANG, J. LIU, M. WANG, X. GUO, B. FAN AND F. WANG 3885
- Heilaohuacid G, a new triterpenoid from *Kadsura coccinea* inhibits proliferation, induces apoptosis, and ameliorates inflammation in RA-FLS and RAW 264.7 cells via suppressing NF- $\kappa$ B pathway**  
Y.-P. YANG, Y.-Q. JIAN, Y.-B. LIU, Q.-L. XIE, H.-H. YU, B. WANG, B. LI, C.-Y. PENG AND W. WANG 3900
- Bryodulcosigenin attenuates bleomycin-induced pulmonary fibrosis via inhibiting AMPK-mediated mesenchymal epithelial transition and oxidative stress**  
Y. DING, L. WANG, B. LIU, G. REN, R. OKUBO, J. YU AND C. ZHANG 3911
- Evaluation of the efficacy of oral nano-silymarin formulation in hospitalized patients with COVID-19: A double-blind placebo-controlled clinical trial**  
H. ARYAN, R. H. FARAHANI, M. CHAMANARA, S. ELYASI, M. R. JAAFARI, M. HADDAD, A. T. SANI, M. A. ARDALAN AND R. MOSAED 3924
- Tanshinone IIA improves contextual fear- and anxiety-like behaviors in mice via the CREB/BDNF/TrkB signaling pathway**  
Y.-L. JIANG, X.-S. WANG, X.-B. LI, A. LIU, Q.-Y. FAN, L. YANG, B. FENG, K. ZHANG, L. LU, J.-Y. QI, F. YANG, D.-K. SONG, Y.-M. WU, M.-G. ZHAO AND S.-B. LIU 3932
- Effects of licorice root supplementation on liver enzymes, hepatic steatosis, metabolic and oxidative stress parameters in women with nonalcoholic fatty liver disease: A randomized double-blind clinical trial**  
P. ROSTAMIZADEH, S. M. K. H. ASL, Z. G. FAR, P. AHMADIJO, T. MAHMUDIONO, D. O. BOKOV, F. ALSAIKHAN, B. JANNAT AND Z. MAZLOOM 3949
- Polysaccharides of *Brassica rapa* L. attenuate tumor growth via shifting macrophages to M1-like phenotype**  
W. GUO, X. LIU, J. GUO, R. GAO, X. XIANG, X. AN AND L. BAI 3957
- Potential mechanism of oral baicalin treating psoriasis via suppressing Wnt signaling pathway and inhibiting Th17/IL-17 axis by activating PPAR $\gamma$**   
Y. CHEN, S. SONG, Y. WANG, J. ZHU AND X. LI 3969
- Molecular dynamics simulation and in vitro evaluation of herb–drug interactions involving dietary polyphenols and CDK inhibitors in breast cancer chemotherapy**  
P. H. PATIL, S. BIRANGAL, G. G. SHENOY, M. RAO, S. KADARI, A. WANKHEDE, H. RASTOGI, T. SHARMA, J. PINJARI AND J. P. CHANNABASAVAIAH 3988
- Olive leaf extract inhibits metastatic melanoma spread through suppression of epithelial to mesenchymal transition**  
P. DE CICCIO, G. ERCOLANO, G. C. TENORE AND A. IANARO 4002



The Notes for Contributors can be found on the journal Home Page at [wileyonlinelibrary.com/journal/ptr](http://wileyonlinelibrary.com/journal/ptr)

## Subscriptions

### Information for subscribers

*Phytotherapy Research* is published in 12 issues per year. Institutional subscription prices for 2022 are: Print & Online: US\$6091 (US and Rest of World), €6091 (Europe), £3933 (UK). Prices are exclusive of tax. Asia-Pacific GST, Canadian GST/HST and European VAT will be applied at the appropriate rates. For more information on current tax rates, please go to [www.wileyonlinelibrary.com/tax-vat](http://www.wileyonlinelibrary.com/tax-vat). The price includes online access to the current and all online back files to January 1<sup>st</sup> 2018, where available. For other pricing options, including access information and terms and conditions, please visit <https://onlinelibrary.wiley.com/library-info/products/price-lists>. Terms of use can be found here: <https://onlinelibrary.wiley.com/terms-and-conditions>

### Delivery Terms and Legal Title

Where the subscription price includes print issues and delivery is to the recipient's address, delivery terms are **Delivered at Place (DAP)**; the recipient is responsible for paying any import duty or taxes. Title to all issues transfers Free of Board (FOB) our shipping point, freight prepaid.

### Claims for Missing or Damaged Print Issues

Our policy is to replace missing or damaged copies within our reasonable discretion, subject to print issue availability, and subject to the following terms: Title to all issues transfers Freight on Board ("FOB") to the address specified in the order; (1) Freight costs are prepaid by Wiley; and (2) Claims for missing or damaged copies must be submitted by the Customer or Subscription Agent within the claims window, as noted below.

### Claims window - General

Claims for missing print issues must be sent to [cs-agency@wiley.com](mailto:cs-agency@wiley.com) (and the Subscription Agent or Customer may be referred to a society) within three months of whichever of these dates is the most recent: date of submission; or date of issue publication.

### Claims window - India

Both Subscription Agents and Customers in India have 48 hours after receipt of goods to confirm that all content listed on the packing label has been received. In the event of any discrepancy, SPUR Infosolutions, Wiley's delivery partner in India, needs to be notified within forty-eight (48) hours using this email address: [support@spurinfo.com](mailto:support@spurinfo.com). All claims will be checked against SPUR Infosolutions delivery records before the claim is accepted. The above terms for Wiley's claims policy otherwise apply.

### Backstock Agent

Back issues: Single issues from current and prior year volumes are available at the current single issue price from [cs-journals@wiley.com](mailto:cs-journals@wiley.com). Earlier issues may be obtained from Periodicals Service Company, 351 Fairview Avenue - Ste 300, Hudson, NY 12534, USA. Tel: +1 518 822-9300, Fax: +1 518 822-9305, Email: [psc@periodicals.com](mailto:psc@periodicals.com)

### Sample Copies

If you are interested in subscribing, you may obtain a free sample copy by contacting John Wiley & Sons, Ltd at the below address.

### Services

#### Advertisements and Bulk Reprints

Advertisement Sales Department, John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, UK.  
Tel: +44 (0) 1243 770351  
Fax: +44 (0) 1243 770432  
E-mail: [adsales@wiley.co.uk](mailto:adsales@wiley.co.uk)

### Reprints

#### Commercial Reprints:

Email: [corporatesaleseurope@wiley.com](mailto:corporatesaleseurope@wiley.com); [corporatesalesusa@wiley.com](mailto:corporatesalesusa@wiley.com); or [corporatesalesaustralia@wiley.com](mailto:corporatesalesaustralia@wiley.com)

#### Author Reprints (50-300 copies):

Order online: [www.sheridan.com/wiley/eoc](http://www.sheridan.com/wiley/eoc)

### Contact details

**Journal Customer Services:** For ordering information, claims and any enquiry concerning your journal subscription please go to [www.wileycustomerhelp.com/ask](http://www.wileycustomerhelp.com/ask) or contact your nearest office:

**Americas:** Email: [cs-journals@wiley.com](mailto:cs-journals@wiley.com); Tel: +1 781 388 8598 or t1 800 835 6770 (toll free in the USA & Canada).

**Europe, Middle East and Africa:** Email: [cs-journals@wiley.com](mailto:cs-journals@wiley.com); Tel: +44 (0) 1865 778315.

**Asia Pacific:** Email: [cs-journals@wiley.com](mailto:cs-journals@wiley.com); Tel: +65 6511 8000.

**Japan:** For Japanese speaking support, Email: [cs-japan@wiley.com](mailto:cs-japan@wiley.com); Tel: +65 6511 8010 or Tel (toll-free): 005 316 50 480.

**Visit our Online Customer Get-Help:** Available in six (6) languages at [www.wileycustomerhelp.com](http://www.wileycustomerhelp.com)

### Pre-Submission English Language Editing

Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English. A list of independent suppliers of editing services can be found at [http://authorservices.wiley.com/bauthor/english\\_language.asp](http://authorservices.wiley.com/bauthor/english_language.asp) Japanese authors can also find a list of local English improvement services at <http://www.wiley.co.jp/journals/editcontribute.html> All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

## Copyright and Copying

Copyright © 2022 John Wiley & Sons, Ltd. All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means without the prior permission in writing from the copyright holder. Authorization to copy items for internal and personal use is granted by the copyright holder for libraries and other users registered with their local Reproduction Rights Organisation (RRO), e.g. Copyright Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, USA ([www.copyright.com](http://www.copyright.com)), provided the appropriate fee is paid directly to the RRO. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works or for resale. Special requests should be addressed to: [permissionsuk@wiley.com](mailto:permissionsuk@wiley.com)

### Disclaimer

The Publisher and the Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher and Editors of the products advertised.

### Abstracting and Indexing

The Journal is indexed by AGRICOLA Database (National Agricultural Library), ASFA: Aquatic Sciences & Fisheries Abstracts (CSA/CIG), BIOBASE (Elsevier), Biological Abstracts® (Thomson ISI), BIOSIS Previews® (Thomson ISI), CAB Abstracts® (CABI), Cambridge Scientific Abstracts (CSA/CIG), Chemical Abstracts Service/SciFinder (ACS), ChemWeb (ChemIndustry.com), CINAHL: Cumulative Index to Nursing & Allied Health Literature (EBSCO), Current Awareness in Biological Sciences (Elsevier), Current Contents®/Life Sciences (Thomson ISI), EMBASE/ Excerpta Medica (Elsevier), Index Medicus/MEDLINE/PubMed (NLM), Journal Citation Reports/ Science Edition (Thomson ISI), Natural Products Update (RSC), PASCAL Database (INIST/CNRS), Science Citation Index Expanded™ (Thomson ISI), Science Citation Index® (Thomson ISI), SCOPUS (Elsevier), SIIC Databases (Sociedad Iberoamericana de Informacion Científica), Web of Science® (Thomson ISI).

### OnlineOpen

Phytotherapy Research accepts articles for Open Access publication. Please visit <http://olabout.wiley.com/WileyCDA/Section/id-406241.html> for further information about OnlineOpen.

### Production Information

For manuscripts that have been accepted for publication, please contact: Devvie Rose Miranda (email: [dmiranda@wiley.com](mailto:dmiranda@wiley.com))  
Printed on acid-free paper.  
Typeset by SPi Global, Philippines  
Printed in Singapore by C.O.S. Printers Pte Ltd.

### Periodical Statement

*PHYTOTHERAPY RESEARCH* (Print ISSN 0951-418X; Online ISSN 1099-1573) is published monthly, total twelve issues, one volume per annum. US mailing agent: Mercury Media Processing, LLC 1850 Elizabeth Avenue, Suite #C, Rahway, NJ 07065 USA. Periodical postage paid at Rahway, NJ. **Postmaster:** Send all address changes to *PHYTOTHERAPY RESEARCH*, John Wiley & Sons Inc., C/O The Sheridan Press, PO Box 465, Hanover, PA 17331.

ISSN 0951-418X (Print)  
ISSN 1099-1573 (Online)

View this journal online at [wileyonlinelibrary.com/journal/ptr](http://wileyonlinelibrary.com/journal/ptr)

### Note to NIH Grantees

Pursuant to NIH mandate, Wiley Blackwell will post the accepted version of contributions authored by NIH grant-holders to PubMed Central upon acceptance. This accepted version will be made publicly available 12 months after publication. For further information, see <http://www.wiley.com/go/nihmandate>

### PEER Project

This journal is participating in the PEER Project, an EU-funded initiative to examine the impact on scholarly journals of depositing accepted manuscripts in web-based repositories. If the corresponding author is based in an EU country, we will deposit the accepted manuscript into the central project repository (DRIVER). The article's availability will be subject to a post-publication embargo. This project has no effect on your rights or obligations under the terms of the copyright agreement pertaining to this journal.

### Wiley's Corporate Citizenship Initiative Statement

Wiley's Corporate Citizenship initiative seeks to address the environmental, social, economic, and ethical challenges faced in our business and which are important to our diverse stakeholder groups. Since launching the initiative, we have focused on sharing our content with those in need, enhancing community philanthropy, reducing our carbon impact, creating global guidelines and best practices for paper use, establishing a vendor code of ethics, and engaging our colleagues and other stakeholders in our efforts.

Follow our progress at [www.wiley.com/go/citizenship](http://www.wiley.com/go/citizenship)

Access to this journal is available free online within institutions in the developing world through the AGORA initiative with the FAO, the HINARI initiative with the WHO and the OARE initiative with UNEP. For information, visit [www.aginternetwork.org](http://www.aginternetwork.org), [www.healthinternetwork.org](http://www.healthinternetwork.org), [www.oaresciences.org](http://www.oaresciences.org)

### Conflict of Interest

All authors must declare financial/commercial conflicts of interest. Even if there is none, this should be stated in a separate paragraph following on from the Acknowledgements section. This is a mandatory requirement for all articles.

# REVIEWS

## Pharmacology of $\alpha$ -spinasterol, a phytosterol with nutraceutical values: A review

Muhammed Majeed, Furkan Ahmad, Lakshmi Mundkur, Subramoniam Appian

Pages: 3681-3690 | First Published: 08 July 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## Medicinal herbs in treating chemotherapy-induced nausea and vomiting: A review

Reza Rajabalizadeh, Mahboobeh Ghasemzadeh Rahbardar, Hossein Hosseinzadeh

Pages: 3691-3708 | First Published: 15 July 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

[Open Access](#)

## The role of selected nutraceuticals in management of prediabetes and diabetes: An updated review of the literature

Giuseppe Derosa, Angela D'Angelo, Pamela Maffioli

Pages: 3709-3765 | First Published: 01 August 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## The effect of flaxseed oil consumption on blood pressure among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized clinical trials

Trias Mahmudiono, Saade Abdalkareem Jasim, Yasir Salam Karim, Dmitry Olegovich Bokov, Walid Kamal Abdelbasset, Kholmurod S. Akhmedov, Ghulam Yasin, Lakshmi Thangavelu, Yasser Fakri Mustafa, Shehla Shoukat, Mazin A.A. Najm, Mohammad Amraei

Pages: 3766-3773 | First Published: 20 July 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## The construction of preclinical evidence for the treatment of liver fibrosis with quercetin: A systematic review and meta-analysis

Xiaochuan Guo, Yuanyuan Li, Weizheng Wang, Luyao Wang, Sihan Hu, Xiaolin Xiao, Caiyu Hu, Yao Dai, Yiheng Zhang, Ziyu Li, Junlin Li, Xiao Ma, Jinhao Zeng

Pages: 3774-3791 | First Published: 02 August 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## The effect of flaxseed intake on appetite reduction: A systematic review of randomized clinical trials

Mahtab Zarei, Shaghayegh Adeli, Shabnam Hosseini, Elnaz Daneshzad

Pages: 3792-3804 | First Published: 02 August 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## Xanthotoxin (8-methoxypsoralen): A review of its chemistry, pharmacology, pharmacokinetics, and toxicity

Anxin Wu, Jing Lu, Guofeng Zhong, Ling Lu, Yan Qu, Chen Zhang

Pages: 3805-3832 | First Published: 01 August 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## Promising natural products against SARS-CoV-2: Structure, function, and clinical trials

Yan Zhao, Shanshan Deng, Yujiao Bai, Jinlin Guo, Guoyin Kai, Xinhe Huang, Xu Jia

Pages: 3833-3858 | First Published: 05 August 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## Crocin molecular signaling pathways at a glance: A comprehensive review

Motahareh Boozari, Hossein Hosseinzadeh

Pages: 3859-3884 | First Published: 21 August 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

# RESEARCH ARTICLES

## Potato protease inhibitor II prevents obesity by inducing browning of white adipose tissue in mice via $\beta_3$ adrenergic receptor signaling pathway

Nana Zhang, Jianlin Liu, Minjie Wang, Xinxin Guo, Bei Fan, Fengzhong Wang

Pages: 3885-3899 | First Published: 26 August 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## Heilaohuacid G, a new triterpenoid from *Kadsura coccinea* inhibits proliferation, induces apoptosis, and ameliorates inflammation in RA-FLS and RAW 264.7 cells via suppressing NF- $\kappa$ B pathway

Yu-pei Yang, Yu-qing Jian, Yong-bei Liu, Qing-ling Xie, Huang-he Yu, Bin Wang, Bin Li, Cai-yun Peng, Wei Wang

Pages: 3900-3910 | First Published: 14 September 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## Bryodulcosigenin attenuates bleomycin-induced pulmonary fibrosis via inhibiting AMPK-mediated mesenchymal epithelial transition and oxidative stress

Yue Ding, Lei Wang, Bei Liu, Guoqing Ren, Ryosuke Okubo, Jing Yu, Chaofeng Zhang





Pages: 3911-3923 | First Published: 06 July 2022

[Abstract](#) | [Full text](#) | [PDF](#) | [References](#) | [Request permissions](#)

---

## REVIEW

# The effect of flaxseed oil consumption on blood pressure among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized clinical trials

Trias Mahmudiono<sup>1</sup> | Saade Abdalkareem Jasim<sup>2</sup> | Yasir Salam Karim<sup>3,4</sup> |  
 Dmitry Olegovich Bokov<sup>5,6</sup>  | Walid Kamal Abdelbasset<sup>7,8</sup> |  
 Kholmurod S. Akhmedov<sup>9</sup> | Ghulam Yasin<sup>10</sup>  | Lakshmi Thangavelu<sup>11</sup> |  
 Yasser Fakri Mustafa<sup>12</sup>  | Shehla Shoukat<sup>13</sup> | Mazin A.A. Najm<sup>14</sup> |  
 Mohammad Amraei<sup>15</sup> 

<sup>1</sup>Department of Nutrition, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia

<sup>2</sup>Al-maarif University College, Medical Laboratory Techniques Department, Al-anbar-Ramadi, Iraq

<sup>3</sup>Department of Pharmacy, Al-Manara College for Medical Sciences, Maysan, Iraq

<sup>4</sup>Department of Pharmacy, Al-Nisour University College, Baghdad, Iraq

<sup>5</sup>Institute of Pharmacy, Sechenov First Moscow State Medical University, Moscow, Russian Federation

<sup>6</sup>Laboratory of Food Chemistry, Federal Research Center of Nutrition, Biotechnology and Food Safety, Moscow, Russian Federation

<sup>7</sup>Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia

<sup>8</sup>Department of Physical Therapy, Kasr Al-Aini Hospital, Cairo University, Giza, Egypt

<sup>9</sup>Professor, Doctor of Medical Sciences, Head of the Department of Internal Diseases No.3, Tashkent Medical Academy, Tashkent, Uzbekistan

<sup>10</sup>Department of Botany, Bahauddin Zakariya University, Multan, Pakistan

<sup>11</sup>Center for Transdisciplinary Research, Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Science, Saveetha University, Chennai, India

<sup>12</sup>Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq

<sup>13</sup>Plant Genomics and Biotechnology, National Institute for Genomics and Advanced Biotechnology, National Agricultural research centre, Islamabad, Pakistan

<sup>14</sup>Pharmaceutical Chemistry Department, College of Pharmacy, Al-Ayen University, Thi-Qar, Iraq

<sup>15</sup>Kuhdasht Health Center, Lorestan University of Medical Sciences, Khorramabad, Iran

## Correspondence

Mohammad Amraei, Kuhdasht Health Center,  
 Lorestan University of Medical Sciences,  
 Khorramabad, Iran.

Email: [amraie.mohammd69@gmail.com](mailto:amraie.mohammd69@gmail.com)

## Abstract

We systematically reviewed randomized clinical trials (RCTs) to elucidate the overall effects of flaxseed oil consumption on blood pressure (BP) in patients with metabolic syndrome and related disorders. PubMed, Scopus, Cochrane Library, and ISI Web of Science databases were systematically searched until March 31, 2020, to find RCTs that examined the effect of flaxseed oil consumption on BP. Weighed mean difference (WMD) was pooled using a random-effects model. Standard methods were used for the assessment of heterogeneity, sensitivity analysis, and publication bias. Meta-analysis of five trials (6 arms) showed significant reductions in systolic (WMD:  $-3.86$  mmHg, 95% CI:  $-7.59$  to  $-0.13$ ,  $p = .04$ ) BP (SBP) after flaxseed oil consumption. However, the overall effect illustrated no significant change in diastolic (WMD:

–1.71 mmHg, 95% CI: –3.67 to 0.26,  $p = .09$ ) BP (DBP) in the intervention group compared with the control group. Our findings revealed that flaxseed oil consumption has favorable effects on SBP in patients with metabolic syndrome and related disorders. However, further investigations are needed to provide more reliable evidence.

#### KEYWORDS

blood pressure, flaxseed, hypertension, meta-analysis, systematic review

## 1 | INTRODUCTION

Hypertension (HTN) is a major risk factor for multiple serious complications such as cardiovascular diseases (CVDs), renal failure, and premature death, which is becoming a worldwide health problem for human beings (Burnier & Egan, 2019; Suhat et al., 2022). The incidence of HT was significantly increased in most countries (37.3% in developed countries and 22.9% in developing countries) owing to rapid urbanization (Guan, Dai, & Wang, 2020). One in four adults worldwide suffers from high blood pressure (BP), and it is estimated that more than 1.5 billion people will have hypertension by 2025 (Council et al., 2013). Different classes of antihypertensive drugs are available; however, good BP control is obtained in less than one-third of patients (Sahebkar, 2014; Saugel & Sessler, 2021). There are still some problems in BP management such as poor medication compliance, medication side effects, and high medication costs (Burnier, Polychronopoulou, & Wuerzner, 2020; Goswami, Sarkar, Bhattacharjee, & Sengupta, 2021; Nies, 1975; Waerber, Burnier, & Brunner, 1999). In recent years, there has been a growing interest and demand for the use of medicinal plants for managing BP reducing the burden of HTN (Ahmad et al., 2018). Previous studies have demonstrated medicinal plants such as ginger (Hasani et al., 2019), garlic (Wang, Yang, Qin, & Yang, 2015), cinnamon (Hadi et al., 2020), and black seed (Sahebkar, 2014) can significantly lower BP. One of the most important herbal medicines which has been widely used is flaxseed.

Flaxseed or linseed (*Linum usitatissimum*), an oilseed crop grown on all continents, was recently acknowledged as a functional food (Basch et al., 2007; Didarkhah, Vatandoost, & Dirandeh, 2020; Hajiahmadi, Hosseinzadeh, & Hosseinzadeh, 2021). Flaxseed gained much attention because of its components (high amounts of  $\alpha$ -linolenic acid [ALA], soluble fiber, lignan, and mucilage) and the potential effect on the prevention of CVDs (Masjedi, Pour, Shokoohinia, & Asgary, 2021; Sahebkar, Katsiki, Ward, & Reiner, 2021). Flaxseed oil has different effects, including anti-inflammatory (Oomah, 2001), anti-chemotactic (Monk et al., 2016), antioxidant (Barthet, Klensporf-Pawlik, & Przybylski, 2014), anti-atherosclerotic (Zanwar, Hegde, & Bodhankar, 2014), and anti-microbial (Mohammed & Hameed, 2018). In addition, flaxseed supplementation produces various potentially protective effects against chronic diseases, such as obesity (Mohammadi-Sartang et al., 2017), dyslipidemia (Hadi et al., 2020), diabetes (Mohammadi-Sartang, Sohrabi, Barati-Boldaji, Raeisi-Dehkordi, & Mazloom, 2018), and metabolic syndrome (Tamtaji et al., 2020). Some trials claimed flaxseed could improve BP in adults (Dodin et al., 2005; Rodriguez-Leyva et al., 2013), whereas

others did not (Billinsky et al., 2013; Dewell, Marvasti, Harris, Tsao, & Gardner, 2011). Therefore, in clinical settings, the effects of flaxseed on BP are controversial.

Previous meta-analyses have shown that flaxseed supplementation can significantly reduce systolic BP (SBP) and diastolic BP (DBP) in adults (Khalesi, Irwin, & Schubert, 2015; Ursoniu et al., 2016). In terms of characteristics of participants, previous meta-analyses have included healthy and unhealthy subjects in their analysis. Healthy status may differently influence the effect of flaxseed oil on BP response. Therefore, it is better to measure the effects of flaxseed separately in these people.

We, therefore, aimed to examine and explore the effect of flaxseed oil on BP in patients with metabolic syndrome and related disorders by performing a systematic review and meta-analysis of all published RCTs.

## 2 | METHODS

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

### 2.1 | Search strategy

Two investigators independently performed a systematic search of the literature across the PubMed, Scopus, Cochrane Library, and ISI Web of Science databases from inception till March 31, 2020, using the following keywords interposed with appropriate Boolean operators: (“flax” OR “linseed” OR “flaxseed oil” OR “lignan” OR “Linum usitatissimum”) AND (“blood pressure” OR “systolic blood pressure” OR “diastolic blood pressure” OR “hypertension”). We further restricted the search to English articles. Additionally, the reference lists of selected studies and relevant reviews were also checked to ensure a complete collection. Discrepancies were resolved through discussion between reviewers until consensus was reached.

### 2.2 | Study selection

After the removal of duplicates, a two-stage screening process consisting of a title and abstract scan and a full-text review was used to



ensure the accurate identification of eligible articles. Human studies were included if they met the following criteria, including: (a) population: adults (age  $\geq 18$  years); (b) intervention: oral supplementation with flaxseed oil compared to control group; (c) outcome: reporting enough data about intended outcomes (SBP and DBP) at baseline and the end of the study in each group; (d) study design: RCTs with parallel design lasting at least for 2 weeks. The exclusion criteria included: (a) non-randomized, non-control, or crossover investigations; (b) RCTs on flaxseed in combination with other herbs or ingredients as a mixture; (c) investigations with healthy participants and (d) studies with a lack of sufficient data required for meta-analysis. Study selection was independently conducted by two reviewers and disagreement was resolved by consensus.

### 2.3 | Data extraction

Data were extracted independently by two authors and entered into a pre-defined table. Collected data included: the first author's name, year of publication, country, intervention sample size, characteristics of the subjects (sex, health status, mean age, and mean body mass index [BMI]), duration of supplementation, and details of the intervention and control groups. Any disagreements were resolved by discussion with a third reviewer. For any missing information, corresponding authors were contacted by email.

### 2.4 | Quality assessment

A systematic assessment of bias in the included study was performed using the Cochrane criteria (Higgins et al., 2011) which included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other biases. We rated each domain of the trials as low risk, unclear, or high risk. Two authors independently conducted the quality assessment. The third author was consulted in case of any disagreement in the appraisal score.

### 2.5 | Statistical analyses

The statistical analysis was undertaken by using the STATA software (StataCorp, College Station, Texas, USA). Differences were expressed as weighted mean differences (WMD) with a 95% confidence interval (CI). To calculate WMDs, means and mean change scores and their standard deviations (SDs) were employed. If only SD for the baseline and final values were provided, SD for the net changes was assigned based on the Follmann method (Follmann, Elliott, Suh, & Cutler, 1992). When the information was reported as standard error (SE), SD was calculated by multiplying SE by the square root of the sample size. Because selected trials were carried out in different settings, the random-effects model was employed to calculate the overall

effect from effect sizes. Statistical heterogeneity among articles was assessed using  $I^2$  statistics. Values of 25%, 50%, and 75% were used for the  $I^2$  analysis and corresponded to low, moderate, and high heterogeneity, respectively (Higgins et al., 2019). To identify potential sources of heterogeneity, a predefined subgroup analysis was conducted based on trial duration, and participant's health status. To investigate whether the results of the meta-analysis were dependent on a particular trial or group of trials, we recomputed the meta-analysis statistic after omitting one study at a time (sensitivity analysis). Given that the effect size of each outcome was less than 10, we were not able to create funnel plots, and the existence of publication bias was inspected only through Egger's regression model.  $p < .05$  were considered statistically significant.

## 3 | RESULTS

### 3.1 | Study selection

Of the 1894 articles identified in the electronic databases, 478 were excluded for being duplicated studies, and 1,399 were excluded for not meeting the eligibility criteria. Ultimately, five studies (6 arms) (Akrami, Nikaein, Babajafari, Faghih, & Yarmohammadi, 2018; Dewell et al., 2011; Kestin, Clifton, Belling, & Nestel, 1990; Paschos et al., 2007; Yang et al., 2018) were included in the meta-analysis. The study selection procedure is outlined in Figure 1.

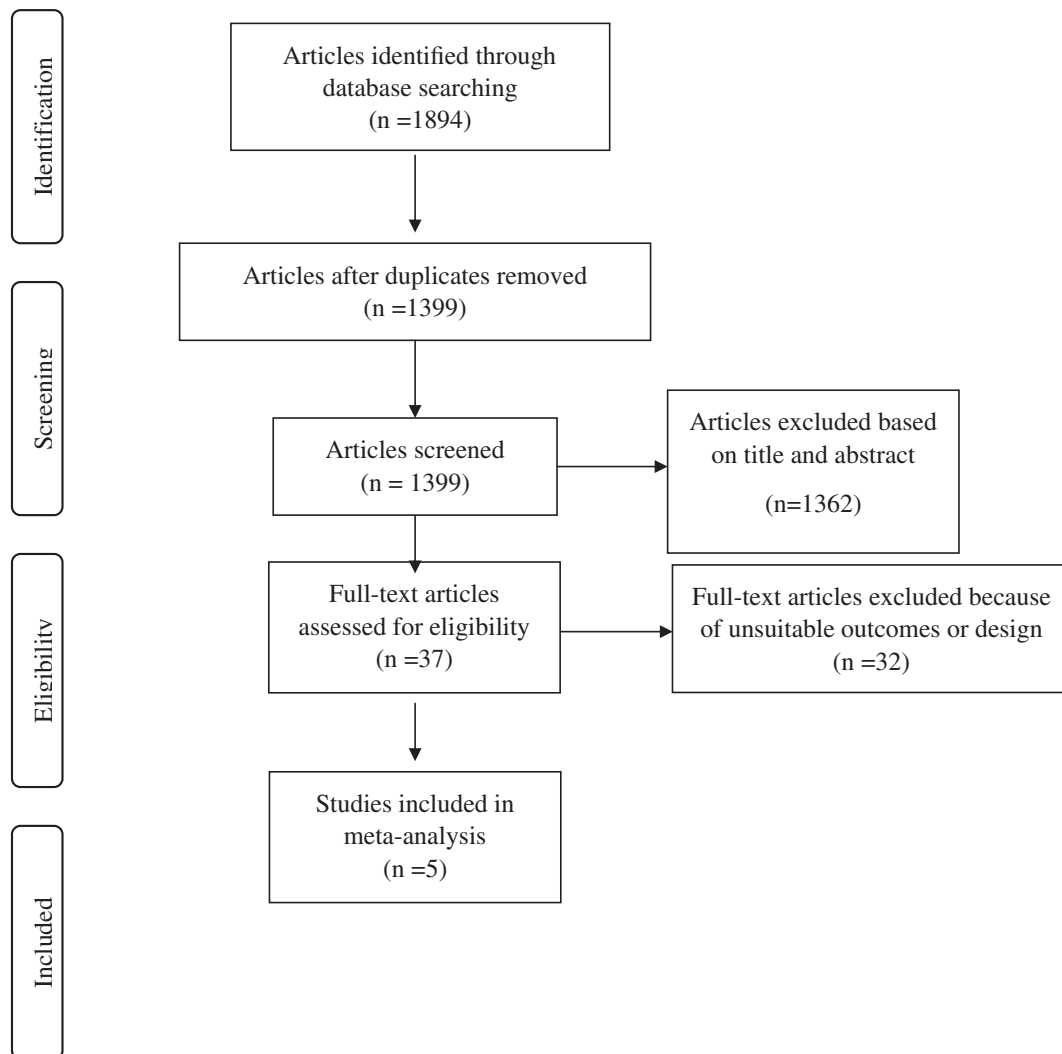
### 3.2 | Study characteristics

The details of the included studies are shown in Table 1. A total of five studies (Akrami et al., 2018; Dewell et al., 2011; Kestin et al., 1990; Paschos et al., 2007; Yang et al., 2018) were included in the systematic review and meta-analysis. The number of participants in these trials ranged from 11 to 42. The included trials were published between 1990 and 2018 and were performed in Iran, the USA, China, Australia, and Greece. Duration of flaxseed oil intake was ranged from six to 12 weeks. The mean age of participants ranged from 49 to 56 years old. Patients' BMI ranged from 26 to 30 Kg/m<sup>2</sup>. Two studies were performed on metabolic syndrome patients, two on subjects with hypercholesterolemia, and one on hypertensive patients. Table 2 reflected the quality of included studies with the risk of bias based on the Cochrane Handbook.

### 3.3 | Meta-analysis

#### 3.3.1 | Effects of flaxseed oil on systolic blood pressure

The overall effect of flaxseed oil consumption on SBP was presented in Figure 2. The results of the random-effects analysis on five included trials (6 arms) showed that flaxseed oil consumption significantly



**FIGURE 1** Flow diagram of the included and excluded studies

**TABLE 1** Characteristics of included studies in the comparison of flaxseed versus control

First author (publication year)	Country	Participant's health status	Interventions sample size	Mean age	Mean BMI (kg/m <sup>2</sup> )	Sex	Intervention of experimental group	Intervention of control group	Duration (weeks)
Akrami et al. (2018)	Iran	Metabolic syndrome	26	49	29	Both	Flaxseed oil/ 25 mL	Sunflower oil	7
Dewell et al. (2011) <sup>a</sup>	USA	Metabolic syndrome	20	50	30	Both	Flaxseed oil/ 6.6 g	Soybean oil	8
Dewell et al. (2011) <sup>b</sup>	USA	Metabolic syndrome	20	51	30	Both	Flaxseed oil/ 2.2 g	Soybean oil	8
Kestin et al. (1990)	Australia	Hypercholesterolemia	11	50	26	Male	Flaxseed oil/ 9.2 g	Safflower oil	6
Paschos et al. (2007)	Greece	Hypercholesterolemia	18	49	28	Male	Flaxseed oil/ 8.1 g	Safflower oil	12
Yang et al. (2018)	China	Hypertensive patients	42	56	26	Both	Flaxseed oil/ 4 g	Corn oil	12

Abbreviation: BMI, Body mass index.

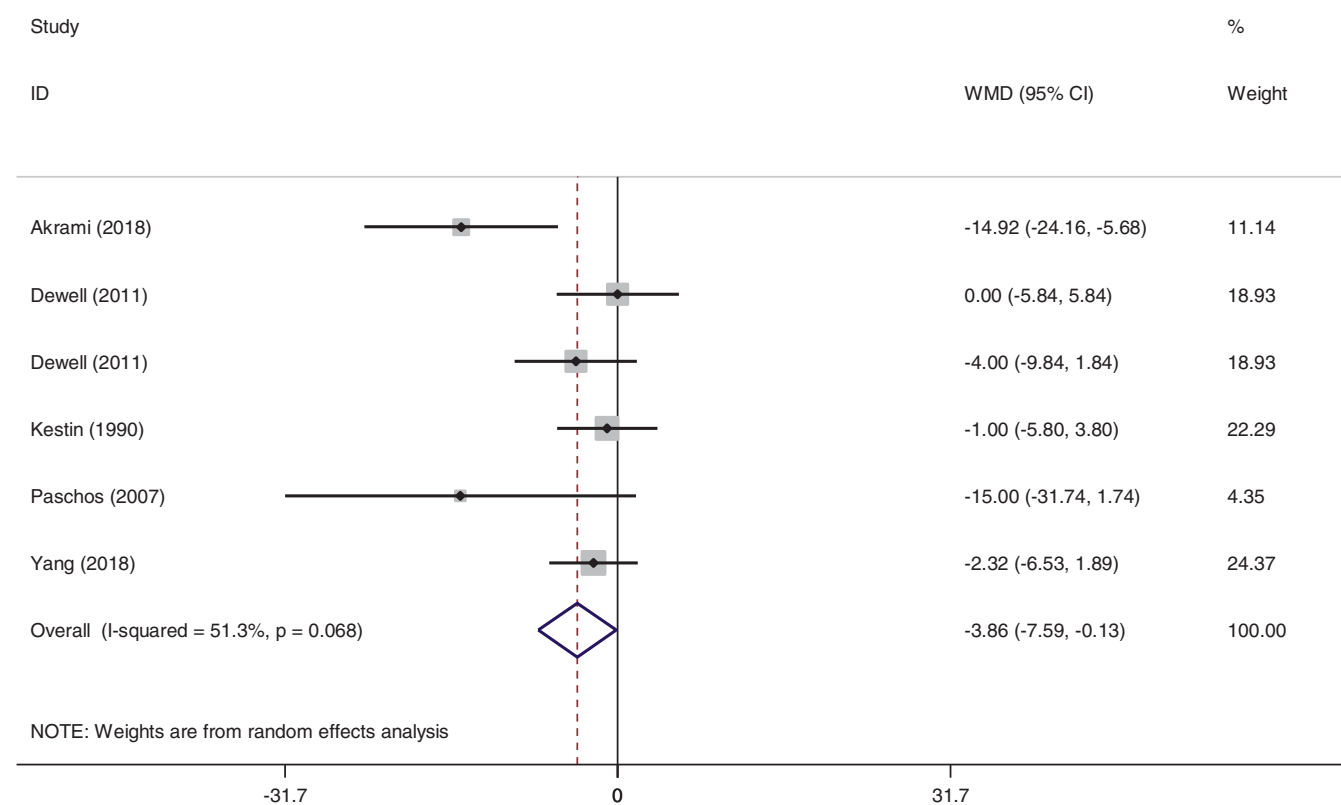
<sup>a</sup>high dose

<sup>b</sup>low dose.

**TABLE 2** Risk of bias assessment for included randomized controlled clinical trials

First author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Akrami et al. (2018)	L	L	U	U	L	L	U
Dewell et al. (2011)	U	U	U	U	L	L	U
Kestin et al. (1990)	U	U	L	L	L	L	U
Paschos et al. (2007)	U	U	L	U	L	L	U
Yang et al. (2018)	L	L	L	L	L	L	U

Abbreviations: H, High risk; L, Low risk; U, Unclear.

**FIGURE 2** Forest plot of the effect of flaxseed oil consumption on systolic blood pressure

reduced SBP (WMD:  $-3.86$  mmHg, 95% CI:  $-7.59$  to  $-0.13$ ,  $p = .04$ ). The heterogeneity between studies was moderate ( $I^2 = 51.3\%$ ,  $p = .06$ ), and could not be eliminated by different subgroup analyses. Also, after classifying the studies based on the health status of the participants and the duration of the intervention, the results were not significant in all subgroups (Supplementary Figures S1 and S2).

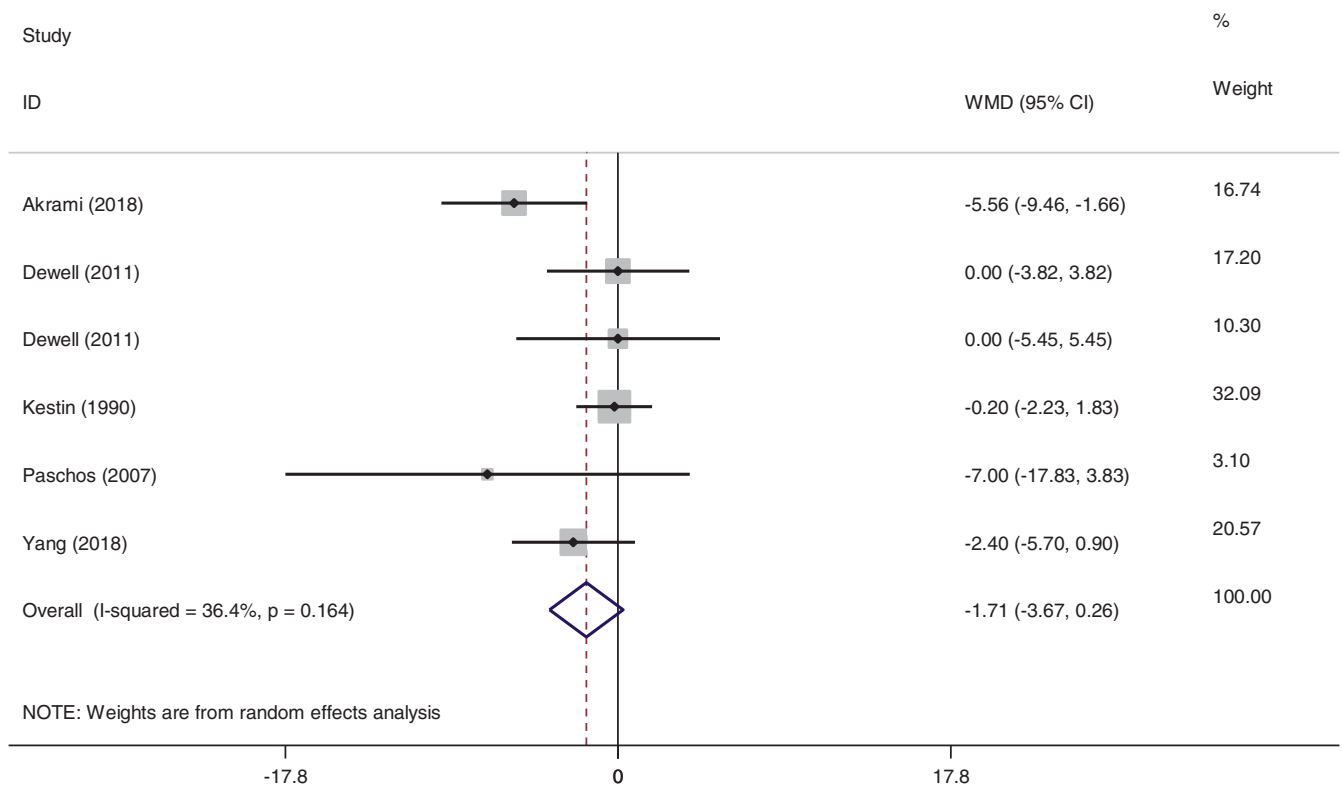
### 3.3.2 | Effects of flaxseed oil on diastolic blood pressure

A total of five studies (6 arms) investigated the effect of flaxseed oil on DBP (Figure 3). We observed that consumption of flaxseed oil could not significantly change DBP compared with the control group

(WMD:  $-1.71$  mmHg, 95% CI:  $-3.67$  to  $0.26$ ,  $p = .09$ ) with a non-significant between-study heterogeneity ( $I^2 = 36.4\%$ ,  $p = .16$ ). Despite classifying the studies based on the duration of the intervention and the health status of the participants, the results remained insignificant in all subgroups (Supplementary Figures S3 and S4).

### 3.3.3 | Sensitivity analysis and publication bias

To explore each study's impact on the overall effect size, we omitted each trial from the analysis step by step. After removing the study by Akrami et al. (WMD:  $-2.12$  mmHg, 95% CI:  $-4.61$  to  $0.35$ ), Dewell et al. (low dose) (WMD:  $-4.15$  mmHg, 95% CI:  $-8.84$  to  $0.53$ ), Paschos et al. (WMD:  $-3.28$  mmHg, 95% CI:  $-6.90$  to  $0.33$ ) and Yang et al. (WMD:



**FIGURE 3** Forest plot of the effect of flaxseed oil consumption on diastolic blood pressure

-4.80 mmHg, 95% CI: -9.89 to 0.27), the overall results of SBP were significantly changed. In addition, eliminating the study by Kestin et al. significantly changed the overall result of DBP (WMD: -2.41 mmHg, 95% CI: -4.77 to -0.05). Furthermore, the results of Egger's regression test indicated no publication bias for SBP ( $p = .06$ ) or DBP ( $p = .31$ ).

## 4 | DISCUSSION

There are several meta-analysis studies that have investigated the effect of flaxseed administration on BP. However, to our knowledge, the present meta-analysis is the first meta-analysis focus on the patients with metabolic syndrome and related disorders. This systematic review and meta-analysis of five clinical trials assessed available evidence about the blood pressure-lowering effect of flaxseed oil in patients with metabolic syndrome and related disorders. The pooled results revealed a significant effect of flaxseed oil in lowering SBP when compared with control. However, we failed to find any significant effect of flaxseed oil consumption on DBP. Results of subgroup analysis regarding DBP revealed that subgroup analysis based on intervention duration, participant's health status could not change their results. The lack of significant benefit of flaxseed oil in subgroup analysis was likely due to limited power, with only 2-3 studies for each subgroup. Indeed, the power of a meta-analysis strongly depends on number of included studies.

Although the amount of SBP reduction found in the current study is modest, a slight reduction of BP may be important in reducing

cardiovascular risk (McInnes, 2005). It has been suggested that SBP is more important than DBP as the CVD risk factor for persons aged over 50 years (Ishii, 2000). It would be useful to perform stratified analysis by hypertension status, but the small number of trials conducted in hypertensive subjects precluded such analysis.

Although the precise mechanisms were not fully understood, the BP-lowering effect of flaxseed oil involves angiotensin converting enzyme inhibition (by the secoisolariciresonol diglucoside) (Prasad, 2013), nitric oxide production (Caligiuri, Edel, Aliani, & Pierce, 2014), and antioxidation and anti-inflammatory activities (Caligiuri et al., 2014; Sahebkar et al., 2021). In addition, flaxseed oil can lower BP due to its dietary fiber, especially soluble fiber, by regulating blood lipids, reducing insulin resistance, and improving the intestinal microbial flora (Anderson et al., 2009; Klosterbuer, Roughhead, & Slavin, 2011). Additionally, dietary fiber appears to improve anthropometric indices, and weight loss can play a role in lowering BP (Jovanovski et al., 2021; Kang, 2021).

Consumption of flaxseed oil has been reported to be safe and well-tolerated in previous investigations, but large doses can cause diarrhea and loose stools. Allergic reactions are also possible. People with coagulation problems, pregnant women, breastfeeding mothers, and children should also be careful in consuming flaxseed oil (Cardoso Carraro, Dantas, Espeschit, Martino, & Ribeiro, 2012; O'keefe, Kapur, Rex, & Watson, 2010; Sahebkar et al., 2021).

A number of certain limitations of our findings should also be acknowledged. Firstly, the results of the current systematic review and meta-analysis were based on relatively small number of studies



and must be interpreted with caution. Secondly, heterogeneity still existed in the trials concerning SBP, which makes our interpretation of the results more complex. Third, the included studies had a short duration, with the majority shorter than 2 months. Therefore, the effect of flaxseed oil supplementation on BP as well as its safety in long term is uncertain. Fourth, confounding factors and their influence were not reported and analyzed in the majority of trials, precluding their analysis in our study. Finally, although formal statistical test did not detect evidence of this bias in our meta-analysis, the power of these tests was limited due to the small number of studies.

## 5 | CONCLUSION

Our findings revealed that flaxseed oil consumption has favorable effects on SBP in patients with metabolic syndrome and related disorders. However, due to limited availability of studies with hypertensive cases and relatively small sample sizes, well-designed RCTs with adequate sample sizes aimed at hypertensive populations are recommended. In addition, the investigators should balance the confounding impact of dietary variety between the intervention and control group and conduct the safety assessment in their studies.

### FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ORCID

Dmitry Olegovich Bokov  <https://orcid.org/0000-0003-2968-2466>

Ghulam Yasin  <https://orcid.org/0000-0002-4923-871X>

Yasser Fakri Mustafa  <https://orcid.org/0000-0002-0926-7428>

Mohammad Amraei  <https://orcid.org/0000-0001-6750-6987>

### REFERENCES

- Ahmad, L., Semotiuk, A. J., Liu, Q.-R., Rashid, W., Mazari, P., Rahim, K., & Sadiq, S. (2018). Anti-hypertensive plants of rural Pakistan: Current use and future potential. *Journal of Complementary Medicine Research*, 7, 138–153.
- Akrami, A., Nikaein, F., Babajafari, S., Faghhi, S., & Yarmohammadi, H. (2018). Comparison of the effects of flaxseed oil and sunflower seed oil consumption on serum glucose, lipid profile, blood pressure, and lipid peroxidation in patients with metabolic syndrome. *Journal of Clinical Lipidology*, 12, 70–77.
- Anderson, J. W., Baird, P., Davis, R. H., Ferreri, S., Knudtson, M., Koraym, A., ... Williams, C. L. (2009). Health benefits of dietary fiber. *Nutrition Reviews*, 67, 188–205.
- Barthet, V. J., Klensporf-Pawlik, D., & Przybylski, R. (2014). Antioxidant activity of flaxseed meal components. *Canadian Journal of Plant Science*, 94, 593–602.
- Basch, E., Mphil, S. B., Collins, J., Dacey, C., Harrison, M., & Szapary, P. (2007). Flax and flaxseed oil (*Linum usitatissimum*): A review by. *Journal of the Society for Integrative Oncology*, 5, 92–105.
- Billinsky, J., Glew, R. A., Cornish, S. M., Whiting, S. J., Thorpe, L. U., Alcorn, J., ... Chilibeck, P. D. (2013). No evidence of hypoglycemia or hypotension in older adults during 6 months of flax lignan supplementation in a randomized controlled trial: A safety evaluation. *Pharmaceutical Biology*, 51, 778–782.
- Burnier, M., & Egan, B. M. (2019). Adherence in hypertension: A review of prevalence, risk factors, impact, and management. *Circulation Research*, 124, 1124–1140.
- Burnier, M., Polychronopoulou, E., & Wuerzner, G. (2020). Hypertension and drug adherence in the elderly. *Frontiers in Cardiovascular Medicine*, 7, 49.
- Caligiuri, S. P., Edel, A. L., Aliani, M., & Pierce, G. N. (2014). Flaxseed for hypertension: Implications for blood pressure regulation. *Current Hypertension Reports*, 16, 1–13.
- Cardoso Carraro, J. C., Dantas, M. I. D. S., Espeschit, A. C. R., Martino, H. S. D., & Ribeiro, S. M. R. (2012). Flaxseed and human health: Reviewing benefits and adverse effects. *Food Reviews International*, 28, 203–230.
- Council, E., Redon, J., Narkiewicz, K., Nilsson, P. M., Burnier, M., Viigimaa, M., ... Schmieder, R. E. (2013). 2013 ESH/ESC guidelines for the management of arterial hypertension. *European Heart Journal*, 34, 2159–2219.
- Dewell, A., Marvasti, F. F., Harris, W. S., Tsao, P., & Gardner, C. D. (2011). Low-and high-dose plant and marine (n-3) fatty acids do not affect plasma inflammatory markers in adults with metabolic syndrome. *The Journal of Nutrition*, 141, 2166–2171.
- Didarkhah, M., Vatandoost, M., & Dirandeh, E. (2020). Effects of flaxseed-rich diet on reproductive performance in estrous-synchronized baluchi ewes. *Archives of Razi Institute*, 75, 397.
- Dodin, S., Lemay, A., Jacques, H., Légaré, F., Forest, J.-C., & Masse, B. (2005). The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: A randomized, double-blind, wheat germ placebo-controlled clinical trial. *The Journal of Clinical Endocrinology & Metabolism*, 90, 1390–1397.
- Follmann, D., Elliott, P., Suh, I., & Cutler, J. (1992). Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology*, 45, 769–773.
- Goswami, B., Sarkar, S., Bhattacharjee, B., & Sengupta, S. (2021). Serum levels of nitric oxide and its correlation with endothelial nitric oxide synthase gene expression among type 2 diabetic patients with or without hypertension: A comparative study in a tertiary care hospital of north East India. *Journal of Natural Science, Biology and Medicine*, 12, 207.
- Guan, Y., Dai, P., & Wang, H. (2020). Effects of vitamin C supplementation on essential hypertension: A systematic review and meta-analysis. *Medicine*, 99, e19274.
- Hadi, A., Askarpour, M., Salamat, S., Ghaedi, E., Symonds, M. E., & Miraghajani, M. (2020). Effect of flaxseed supplementation on lipid profile: An updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials. *Pharmacological Research*, 152, 104622.
- Hadi, A., Campbell, M. S., Hassani, B., Pourmasoumi, M., Salehi-Sahlabadi, A., & Hosseini, S. A. (2020). The effect of cinnamon supplementation on blood pressure in adults: A systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition ESPEN*, 36, 10–16.
- Hajiahmadi, S., Hosseinzadeh, E., & Hosseinzadeh, M. (2021). Flaxseed and its products improve glycemic control: A systematic review and meta-analysis. *Obesity Medicine*, 22, 100311.
- Hasani, H., Arab, A., Hadi, A., Pourmasoumi, M., Ghavami, A., & Miraghajani, M. (2019). Does ginger supplementation lower blood pressure? A systematic review and meta-analysis of clinical trials. *Phytotherapy Research*, 33, 1639–1647.

- Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, *343*, d5928.
- Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2019). *Cochrane handbook for systematic reviews of interventions*. Hoboken: John Wiley & Sons.
- Ishii, M. (2000). The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure, and 1999 world health organization-international society of hypertension guidelines for the management of hypertension. *Nihon rinsho. Japanese Journal of Clinical Medicine*, *58*, 267–275.
- Jovanovski, E., Mazhar, N., Komishon, A., Khayyat, R., Li, D., Blanco Mejia, S., ... Sievenpiper, J. L. (2021). Effect of viscous fiber supplementation on obesity indicators in individuals consuming calorie-restricted diets: A systematic review and meta-analysis of randomized controlled trials. *European Journal of Nutrition*, *60*, 101–112.
- Kang, N. L. (2021). Association between obesity and blood pressure in common Korean people. *Vascular Health and Risk Management*, *17*(371), 377.
- Kestin, M., Clifton, P., Belling, G. B., & Nestel, P. (1990). N-3 fatty acids of marine origin lower systolic blood pressure and triglycerides but raise LDL cholesterol compared with n-3 and n-6 fatty acids from plants. *The American Journal of Clinical Nutrition*, *51*, 1028–1034.
- Khalesi, S., Irwin, C., & Schubert, M. (2015). Flaxseed consumption may reduce blood pressure: A systematic review and meta-analysis of controlled trials. *The Journal of Nutrition*, *145*, 758–765.
- Klosterbuer, A., Roughead, Z. F., & Slavin, J. (2011). Benefits of dietary fiber in clinical nutrition. *Nutrition in Clinical Practice*, *26*, 625–635.
- Masjedi, M. S., Pour, P. M., Shokoohinia, Y., & Asgary, S. (2021). Effects of flaxseed on blood lipids in healthy and Dyslipidemic subjects: A systematic review and meta-analysis of randomized controlled trials. *Current Problems in Cardiology*, *47*, 100931.
- McInnes, G. T. (2005). Lowering blood pressure for cardiovascular risk reduction. *Journal of Hypertension*, *23*, S3–S8.
- Mohammadi-Sartang, M., Sohrabi, Z., Barati-Boldaji, R., Raeisi-Dehkordi, H., & Mazloom, Z. (2018). Flaxseed supplementation on glucose control and insulin sensitivity: A systematic review and meta-analysis of 25 randomized, placebo-controlled trials. *Nutrition Reviews*, *76*, 125–139.
- Mohammadi-Sartang, M., Mazloom, Z., Raeisi-Dehkordi, H., Barati-Boldaji, R., Bellissimo, N., & Totosy De Zepetnek, J. (2017). The effect of flaxseed supplementation on body weight and body composition: A systematic review and meta-analysis of 45 randomized placebo-controlled trials. *Obesity Reviews*, *18*, 1096–1107.
- Mohammed, G. J., & Hameed, I. H. (2018). *Linum usitatissimum*: Antibacterial activity, chromatography, bioactive compounds, applications: A review. *Indian Journal of Public Health Research and Development*, *9*, 375–380.
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151*, 264–269.
- Monk, J. M., Liddle, D. M., Brown, M. J., Zarepoor, L., De Boer, A. A., Ma, D. W., ... Robinson, L. E. (2016). Anti-inflammatory and anti-chemotactic effects of dietary flaxseed oil on CD8<sup>+</sup> T cell/adipocyte-mediated cross-talk. *Molecular Nutrition & Food Research*, *60*, 621–630.
- Nies, A. S. (1975). Adverse reactions and interactions limiting the use of antihypertensive drugs. *The American Journal of Medicine*, *58*, 495–503.
- O'keefe, A., Kapur, S., Rex, G., & Watson, W. (2010). Flax seed allergy in children: An emerging allergen? *Allergy, Asthma & Clinical Immunology*, *6*(1–1), 4.
- Oomah, B. D. (2001). Flaxseed as a functional food source. *Journal of the Science of Food and Agriculture*, *81*, 889–894.
- Paschos, G. K., Zampelas, A., Panagiotakos, D. B., Katsiogiannis, S., Griffin, B. A., Votteas, V., & Skopouli, F. N. (2007). Effects of flaxseed oil supplementation on plasma adiponectin levels in dyslipidemic men. *European Journal of Nutrition*, *46*, 315–320.
- Prasad, K. (2013). Secoisolariciresinol diglucoside (SDG) isolated from flaxseed, an alternative to ACE inhibitors in the treatment of hypertension. *International Journal of Angiology*, *22*, 235–238.
- Rodriguez-Leyva, D., Weighell, W., Edell, A. L., Lavalley, R., Dibrov, E., Pinneker, R., ... Guzman, R. (2013). Potent antihypertensive action of dietary flaxseed in hypertensive patients. *Hypertension*, *62*, 1081–1089.
- Sahebkar, A. (2014). A systematic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels. *Clinical Nutrition*, *33*, 406–414.
- Sahebkar, A., Katsiki, N., Ward, N., & Reiner, Ž. (2021). Flaxseed supplementation reduces plasma lipoprotein (a) levels: A meta-analysis. *Alternative Therapies in Health & Medicine*, *27*(223), 239.
- Saugel, B., & Sessler, D. I. (2021). Perioperative blood pressure management. *Anesthesiology*, *134*, 250–261.
- Suhat, S., Suwandono, A., Adi, M. S., Nugroho, H., Widjanarko, B., & Wahyuni, C. U. (2022). Relationship between health belief model and the medical adherence and risk factors prevention of hypertension patients in Cimahi City Indonesia. *Evidence Based Care*, *12*, 51–56.
- Tamtaji, O. R., Milajerdi, A., Reiner, Ž., Dadgostar, E., Amirani, E., Asemi, Z., ... Sadoughi, F. (2020). Effects of flaxseed oil supplementation on biomarkers of inflammation and oxidative stress in patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition ESPEN*, *40*, 27–33.
- Ursoniu, S., Sahebkar, A., Andrica, F., Serban, C., Banach, M., & Lipid and Blood Pressure Meta-analysis Collaboration. (2016). Effects of flaxseed supplements on blood pressure: A systematic review and meta-analysis of controlled clinical trial. *Clinical Nutrition*, *35*, 615–625.
- Waeber, B., Burnier, M., & Brunner, H. (1999). Compliance with antihypertensive therapy. *Clinical and Experimental Hypertension*, *21*, 973–985.
- Wang, H. P., Yang, J., Qin, L. Q., & Yang, X. J. (2015). Effect of garlic on blood pressure: A meta-analysis. *The Journal of Clinical Hypertension*, *17*, 223–231.
- Yang, B., Shi, L., Wang, A.-M., Shi, M.-Q., Li, Z.-H., Zhao, F., ... Li, D. (2018). Lowering effects of n-3 fatty acid supplements on blood pressure by reducing plasma angiotensin II in Inner Mongolia hypertensive patients: A double-blind randomized controlled trial. *Journal of Agricultural and Food Chemistry*, *67*, 184–192.
- Zanwar, A. A., Hegde, M. V., & Bodhankar, S. L. (2014). Flax lignan in the prevention of atherosclerotic cardiovascular diseases. In *Polyphenols in human health and disease*. Amsterdam: Elsevier.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Mahmudiono, T., Jasim, S. A., Karim, Y. S., Bokov, D. O., Abdelbasset, W. K., Akhmedov, K. S., Yasin, G., Thangavelu, L., Mustafa, Y. F., Shoukat, S., Najm, M. A. A., & Amraei, M. (2022). The effect of flaxseed oil consumption on blood pressure among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized clinical trials. *Phytotherapy Research*, 1–8. <https://doi.org/10.1002/ptr.7566>