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Paul C. Guest *Editor*

Studies on Biomarkers and New Targets in Aging Research in Iran

Focus on Turmeric and Curcumin

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Preface

The Middle East is known as the cradle of civilization. It was the crossroads of ancient empires and the birthplace of major world religions. Today it is the center of many world issues due to its economic, religious, and political importance. Although it has lagged behind many other regions of the world in medicinal research, this has increased dramatically in recent years with increasing numbers of relevant publications, and the country of Iran has spearheaded this progress. Much of the research has focused on increasing our understanding of the aging process and attempting to identify biomarkers and natural products to improve the human health span. This book provides a comprehensive overview of the research conducted in the Middle East on the health benefits of curcumin, a phytochemical derived from the famous spice turmeric. Hundreds of studies have now been published describing the health benefits of this spice. The importance of this research is exemplified by poor data regarding health and longevity as only 0.08% of the population in Iran consists of individuals over 90 years of age. This is approximately 10 times lower than the percentage of this same age group in the United Kingdom and the United States of America and almost 20 times lower than that in Japan.

This book presents a series of reviews and meta-studies describing research which has resulted in identification of potential new biomarkers and drug targets for age-related disorders. All of the studies have focused on the testing of curcumin and related products, which have already shown some promising leads in age-related conditions such as heart disease, diabetes, cognitive impairment, and cancer. The authors in this series come from different centers and cities of Iran, including Mashhad, Tehran, Isfahan, Ahvaz, Birjand, Quchan, and Yazd, and many of the chapters feature collaborations with other countries of the Middle East and throughout the world, including Brazil, Italy, Mexico, Oman, Poland, Switzerland, the United Kingdom, and the United States of America. This underscores the emergence of the Middle East into this arena of research.

The book will be of high interest to scientific and clinical researchers in the subject of aging and age-related disease, and to physicians and pharmaceutical company scientists since it gives insights into the latest strategies, biomarkers, and targets involved in the mechanism of action of curcumin to promote healthy aging. It will also provide important information on disease mechanisms related to age-related disorders as each chapter will be presented in the context of specific chronic diseases.

Sao Paulo, Brazil | Paul C. Guest

Contents

1 Research in the Middle East into the Health Benefits of Curcumin

Paul C. Guest and Amirhosein Sahebkar

Abstract

The Middle East is known as the cradle of civilization. It was the crossroads of ancient empires and the birthplace of major world religions. Today, it is the center of many world issues due to economic, religious, and political reasons. Although it has lagged behind many other regions of the world in medicinal research, this has increased dramatically in recent years with increasing numbers of relevant publications. Much of this research has focused on increasing our understanding of the aging process and attempting to identify biomarkers and natural products to improve the human health span. This review provides a brief overview of the research conducted in the Middle East on the health benefits of curcumin, a phytochemical derived from the famous spice turmeric. These efforts have been mainly spearheaded by Iran.

Keywords

Middle East · Iran · Turmeric · Curcumin · Research · Clinical trial · New drug targets

1.1 Introduction

The Middle East is known as the birthplace of civilizations and has always served as crossroads of world cultures and religions. The official countries recognized by the United Nations as being part of the Middle East are Bahrain, Cyprus, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates (UAE), and Yemen, although this can vary depending on the source and can include other countries from Africa and Asia (Fig. 1.1) (Table 1.1). The largest of the countries listed above in terms of area is Saudi Arabia at 2,149,690 km^2 and the smallest is Bahrain at 780 km^2. In terms of population, Egypt has the largest number at approximately 82,798,000 people and Cyprus has the smallest with 1,088,503 people [1].

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Fig. 1.1 The Middle East. UAE: United Arab Emirates

Table 1.1 Middle East countries in terms of area and population

Country	Area (km^2)	Population
Bahrain	780	1,701,582
Cyprus	9250	1,207,360
Egypt	1,010,407	102,334,403
Iran	1,648,195	83,992,953
Iraq	438,317	40,222,503
Israel	20,770	8,655,540
Jordan	92,300	10,203,139
Kuwait	17,820	4,270,563
Lebanon	10,452	6,825,441
Oman	212,460	5,106,622
Qatar	11,437	2,881,060
Saudi Arabia	2,149,690	34,813,867
Syria	185,180	17,500,657
Turkey	783,562	84,339,067
United Arab Emirates	82,880	9,890,400
Yemen	527,970	29,825,968

Consistent with the rest of the world, the proportion of aged people (≥65 years-old) has increased dramatically in recent years in most of these countries [1, 2]. Table 1.2 shows the population over 65 years old in each country in the Middle East in terms of total number and percentage relative to the total population of that country. This shows that Turkey has the greatest number of individuals over the age of 65 years at 7,574,551 and Qatar has the lowest at 48,663 per-

Table 1.2 Middle East countries in terms of population over 65 years old and change since the year 2000

Country	Population ≥ 65 years old	% Population ≥ 65 years old	2020:2000 ≥ 65 years old ratio
Bahrain	874,118	2.93	1.08
Cyprus	173,965	14.41	1.41
Egypt	5,456,144	5.33	1.08
Iran	5,513,595	6.56	1.50
Iraq	1,384,755	3.44	0.99
Israel	1,074,531	12.41	1.24
Jordan	403,405	4.00	1.29
Kuwait	129,642	3.03	1.92
Lebanon	515,256	7.54	1.32
Oman	128,229	2.51	1.03
Qatar	48,663	1.69	0.97
Saudi Arabia	1,217,949	3.50	1.17
Syria	853,060	4.87	1.46
Turkey	7,574,551	9.00	1.47
United Arab Emirates	125,051	1.26	1.16
Yemen	767,679	2.57	1.05

sons. However, Cyprus has the highest proportion of individuals in the "over 65 age" group at 14.41% of the total population and the UAE has the lowest at 1.26%. In addition, Kuwait has seen the largest increase in the proportion of the "over 65 age" group since the year 2000 at 1.92-fold (2020 compared with 2000), followed by Iran, Turkey, and Syria at 1.50-, 1.47-, and 1.46-fold, respectively (Table 1.2).

In line with this aging population trend, medical expenses are expected to rise due to the increased prevalence of age-related diseases and associated disabilities [3]. Thus, there are increased efforts by researchers and clinicians to come up with widely generalizable preventive and therapeutic approaches to reduce the burden of diseases such as type 2 diabetes mellitus, cardiovascular disorders, Alzheimer's disease, frailty, and cancer [4]. Complementary and alternative medicine has a long history of use in the Middle East countries, and there are rich anecdotal and traditional medicine reports on the widespread use and efficacy of herbal medicines for a variety of diseases in this region. During the recent decades, overwhelming evidence from well-designed pharmacological and clinical studies has corroborated the traditional uses of medicinal plants and their active ingredients (phytochemicals) in different pathologies [5].

Among the vast numbers of herbal medicines, turmeric (*Curcuma longa* L.) has received a considerable reputation in recent years given its well-known pharmacological and healing properties [5]. It has been used in traditional medicine in parts of Asia and the Middle East for more than 4000 years. There are reports of its use in the Vedic culture in India dating back to 2500 BC. Also, it appeared as part of Ayurvedic medicine around 500 BC and this is still practiced today. Inhalation of burning turmeric fumes has been claimed to relieve congestion, and the topical application of turmeric juice or paste was thought to help in the wound healing process. Just two centuries ago, Vogel and Pelletier reported the isolation of a "yellow-colored matter" from the rhizomes of turmeric which they called curcumin [6]. In 1910, Milobedzka and Lampe identified the chemical structure of curcumin as 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E) (Fig. 1.2) [7]. It was not until 1949 that curcumin first appeared in the scientific literature in a significant way through the finding that it had bacteriostatic properties [8].

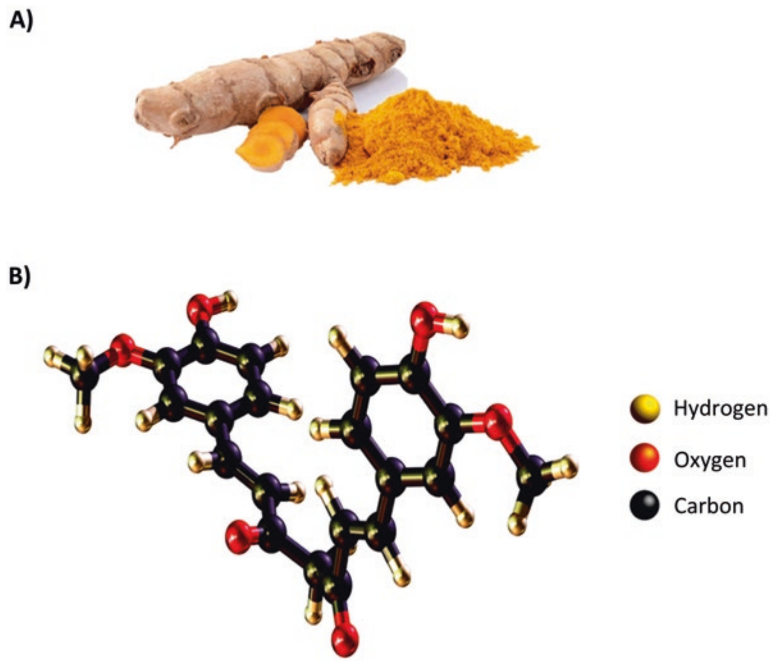

Fig. 1.2 (**a**) Turmeric rhizomes and powder. (**b**) Structure of curcumin

This review describes some of the emerging potential medicinal uses for curcumin and the role that the Middle East has played in these studies. In addition, it will discuss the current health issues in these countries as well as the research taking place there into the potential therapeutic uses of curcumin.

1.2 Current Uses

Turmeric is thought to have originated in India, the largest producer and consumer of this spice in the world (Fig. 1.3a). Almost 80% of the world's turmeric is produced in India, with the remaining 20% produced in China, Myanmar, Bangladesh, Nigeria, and others [9]. Economically, it is important due to its many uses and it is exported throughout the world. The turmeric plant is cultivated and propagated via its rootstalk in hot and humid climates at low to medium altitudes (up to 1200 m). The plant is harvested by digging up the rhizomes when the leaves start to turn yellow (approximately 8 months after plantation). The top importers of this spice are the United States of America (USA) (29%), followed by Iran (15%) and the UAE (10%), with Malaysia, Morocco, the United Kingdom (UK), Sri Lanka, Germany, Japan, and Saudi Arabia accounting for most of the remaining 46% of the imports (Fig. 1.3b) [10].

Turmeric is perhaps best known as a major ingredient of curries and is also known for its use as a dye, and for applications in the cosmetic and pharmaceutical industries [11]. Turmeric has attracted considerable interest over recent decades as it contains the curcuminoids, curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which have bioactivity. Consumption of curcumin appears to be safe and confer beneficial effects against multiple chronic diseases [12, 13], including obesity, metabolic syndrome, diabetes, various cancers, fatty liver disease, major depression, Alzheimer's disease, and arthritis. Thus far, no precise conclusions can be made and thus additional large-scale, well-designed clinical studies are required which also take into account potential confounding factors specific for each disease/medical area. A major consideration has concerned the low aqueous solubility and oral bioavailability of curcumin [14]. With this in mind, several approaches have now been developed to increase curcumin's bioavailability, including the use of curcumin analogues [15], hyaluronic acid composite microneedles containing curcumin-

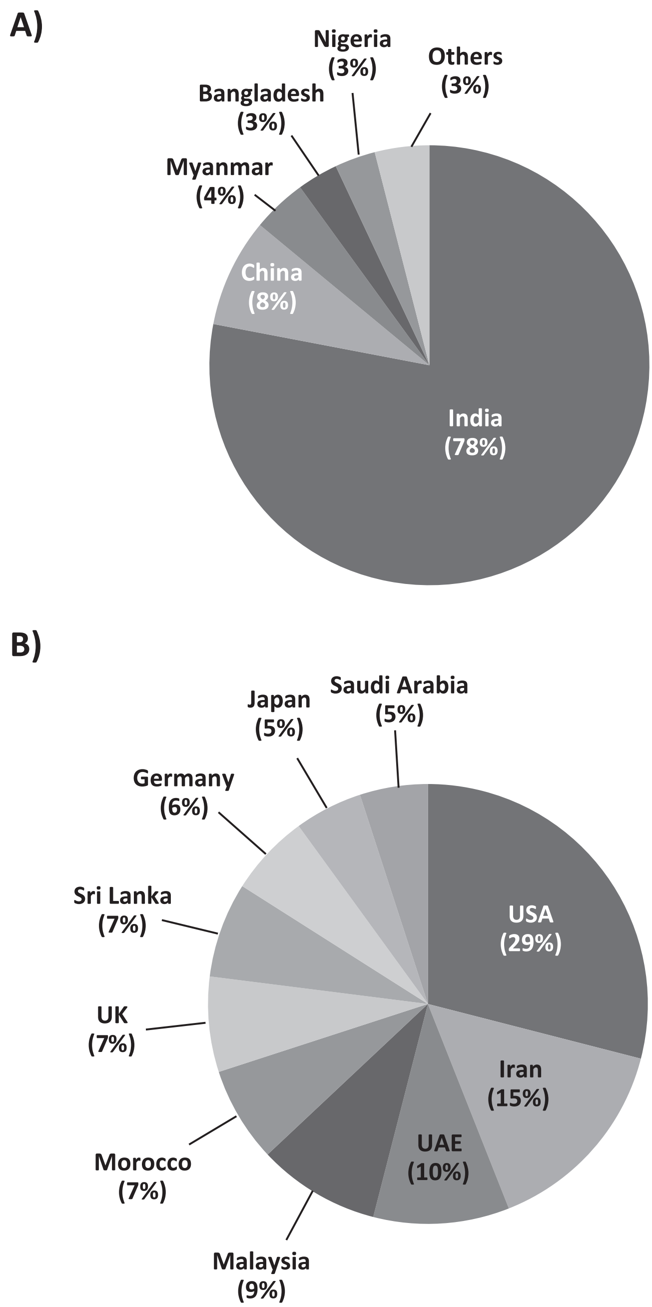

Fig. 1.3 Top (**a**) producers and (**b**) importers of turmeric in the world

loaded micelles [16], different types of bio-nano-carriers [17], and encapsulation in liposome nanocarriers [18].

A number of studies have now been conducted which aimed to determine the molecular mechanism of curcumin function in health and disease, as a means of finding molecular targets as well as the pharmacological profile and interactions of this phytochemical [19]. In tumor cells, curcumin regulates the cell cycle, reactive oxygen species (ROS) generation, cytosolic Ca^{2+} levels, nuclear factor kappa B (NF-κB) signaling, and cytokine responses. In turn, this triggers endoplasmic reticulum (ER) and mitochondrial stress, leading to reduction in cancer cell propagation or increased apoptosis and/or death. In addition, curcumin can cross the blood brain barrier, enabling the protection of neurons from oxidative stress and inflammatory damage. It has also been found that curcumin may alleviate diseases such as rheumatoid arthritis [20], cardiac hypertrophy [21], breast cancer [22], and non-small cell lung cancer (NSCLC) [23], via inhibition of the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway was first described as a regulator of G1- to S-phase transition in eukaryotic cells [24] and is now well known as a promising target in cancer in multiple disease areas as well as in the aging process [25–28].

1.3 The Growth in Curcumin Research in the Middle East

A PubMed search using the terms "curcumin" and "Bahrain" or "Cyprus" or "Egypt" or "Iran" or "Iraq" or "Israel" or "Jordan" or "Kuwait" or "Lebanon" or "Oman" or "Qatar" or "Saudi Arabia" or "Syria" or "Turkey" or "United Arab Emirates" or "Yemen" showed that Iran had the most publications since Jan 01, 2005 to the present day (Feb 24 at the time of the search) with 795, followed by Turkey with 238, Egypt with 233, Saudi Arabia with 156, and Israel with 98. The large number of publications on the subject of curcumin from Iran can be attributed to a steady increase from the year 2011 (Fig. 1.4). The number of publications by Iran over this time is only exceeded by China, The United States of America, and India at 3263, 1989, and 1941, respectively. However, if this value is normalized according to population size, the publication rates in this field are highest for Iran (9.47 per million people) and lowest for India (1.41 per million people) (Table 1.3).

In Iran alone, the last 10 research articles have shown positive effects of curcumin in disease areas such as rheumatoid arthritis [29], wound healing [30], ulcerative colitis [31], non-alcoholic fatty liver disease [32–34], diabetes cell therapy [35], osteoarthritis [36], endodontic infection [37], and insulin resistance [38]. In addition, recent research has attempted to address the low bioavailability issue through the development of different curcumin formulations or delivery systems [39–48]. These have been tested mainly in disease or medical areas such as cancer [39, 43, 45–48], wound healing [40], malaria [41], drug delivery [42], and polycystic ovary syndrome [44]. Further research at both the preclinical and clinical levels is required in order to determine the most efficacious delivery systems for each specific disease area.

1.4 The Health Situation in the Middle East

As with most of the rest of the world, there should be a focus on improved nutrition due to the rising obesity epidemic in the Middle East. Strikingly, 8 countries from the Middle East (Kuwait, Jordan, Saudi Arabia, Qatar, Turkey, Lebanon, Egypt, and the UAE) have been ranked as having the highest adult obesity prevalence out of the top 20 most obese countries in the world (the top 10 positions are occupied by Pacific Island nations or territories: Nauru; Cook Islands; Palau; Marshall Islands; Tuvalu; Niue; Tonga; Samoa; Kiribati; and Micronesia) [49]. Therefore, research into natural dietary solutions such as supplementation with curcumoids is essential in the Middle East. In the sections below, the health needs of each of country are presented in terms the highest causes of death and disability combined, as well as the highest risk factors which may have contributed to these. All of the information is based on 2017 statistics from the Institute for Health Metrics and Evaluation (IHME), an independent global health research center at the University of Washington, Seattle, WA, USA [50]. The data regarding body mass index (BMI) was obtained from IndexMundi [51] and were all recorded in 2016.

1.4.1 Bahrain

In Bahrain, the highest cause of death and disability was diabetes, followed by ischemic heart disease, low back pain, headache disorders, drug use disorders, and depressive disorders. Not sur-

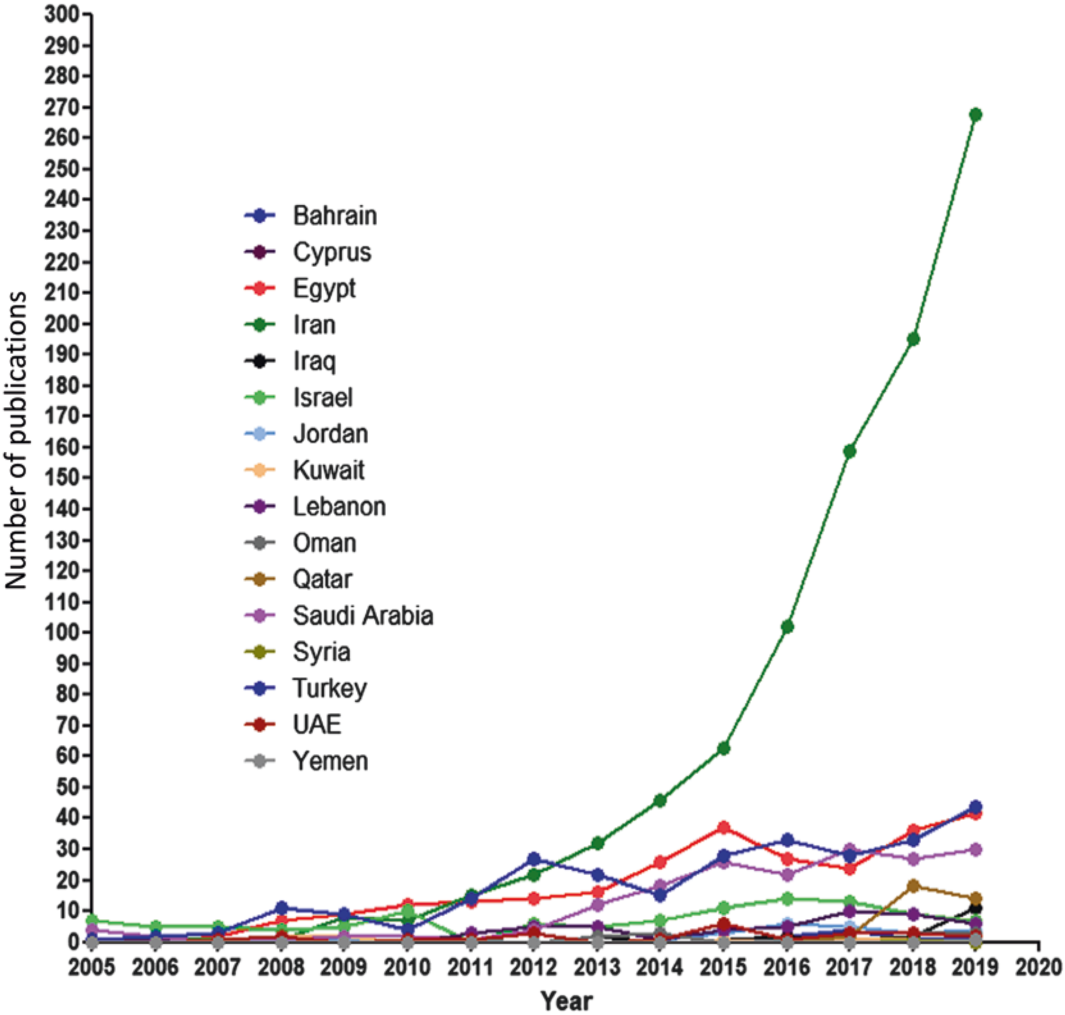

Fig. 1.4 Number of publications from Jan 1, 2005 to Dec 31, 2019 indexed on PubMed per country in the Middle East

Table 1.3 Number of publications regarding curcumin research per one million people from Jan 01, 2005 to Feb 24, 2020

Country	Total number of publications	Publications/million people
China	3263	2.27
India	1941	1.41
Iran	795	9.47
USA	1989	6.01

prisingly, the main risk factors driving this were high BMI, high fasting plasma glucose, dietary risks, high blood pressure (BP), and tobacco use. The data regarding BMI as having the highest risk association with the causes of death and disability is consistent with the obesity rate in 2016 amounting to 29.8% of the adult population.

1.4.2 Cyprus

In Cyprus, ischemic heart disease was the number one cause of death and disability combined, followed by low back pain, diabetes, headache disorders, stroke, and lung cancer. The main risk factors which drove these were tobacco use, high fasting plasma glucose, dietary risks, high BP, and BMI. In 2016 the adult obesity prevalence was 21.8%, consistent with the finding that high BMI was not the highest driver of deaths and disability. The statistic showing that tobacco use was the highest risk factor is likely to be linked to the fact that Cyprus has one of the highest tobacco consumption rates in Europe [52].

1.4.3 Egypt

Ischemic heart disease was the top-ranked cause of death and disability followed by road injuries, lower respiratory infection, stroke, neonatal disorders, and cirrhosis. This was linked with the top risk factor of deleterious diets, followed by high BP, high BMI, high fasting plasma glucose, and tobacco use. The main risks of poor diet, high BP and high BMI, are consistent with the observation that the adult obesity prevalence was 32% in 2016. This translated to Egypt being the 19th most obese nation in the world. To account for death and disability due to road accidents, Egypt reports approximately 0.42 deaths per 1000 people due to traffic accidents, and pedestrians account for approximately 20% of these fatalities [53].

1.4.4 Iran

The leading causes of death and disability in Iran were ischemic heart disease, neonatal disorders, road injuries, headache disorders, low back pain, and drug use disorders. In terms of risk factors, these were driven mostly by high BP, dietary risks, high fasting plasma glucose, high BMI, and tobacco use. The adult obesity prevalence in Iran was 25.8%. These factors are linked to the rising epidemic in cardiovascular diseases and may be related to socioeconomic and nutritional changes, combined with inadequate physical activity levels [54]. Thus, nutrition and exercise-based strategies to promote health and control these risk factors are essential to reduce the burden of this disease.

1.4.5 Iraq

The leading causes of death in Iraq were markedly different from the other countries. In descending order these were conflict and terror, neonatal disorders, congenital defects, ischemic heart disease, stroke, and headache disorders. These were linked to malnutrition, dietary risks, high BMI, BP, and fasting plasma glucose. The adult obesity prevalence was 30.4% which accounts for the metabolic-related risk factors. The cause of death or disability due to conflict and terror is most likely an outcome of the various wars that have plagued the region since 2003 [55].

1.4.6 Israel

In Israel, the main cause of death and disability was low back pain and headache disorders, followed by ischemic heart disease, diabetes, depressive disorders, and blindness and vision impairment. These appeared to be linked to the same causative factors as for most other countries in the Middle East with high fasting plasma glucose contributing the highest risk, followed by tobacco use, high BMI, high BP, and dietary risks. The adult obesity prevalence rate was 26.1% which was marginally lower than other Middle East countries apart from Iran and Yemen (see below). This may account for the fact that metabolic disorders were not the leading cause of death or disability.

1.4.7 Jordan

The main cause of death and disability in Jordan was neonatal disorders, followed by congenital defects, ischemic heart disease, headache disorders, low back pain, and diabetes. The main risk factors associated with these were malnutrition, high BMI, high fasting plasma glucose, dietary risks, and high BP. The obesity prevalence rate was relatively high in Jordan at 35.5%, leading to its ranking as the 13th most obese nation in the world.

These findings are most likely due to a shift from undernutrition to one of overnutrition which has led to premature morbidities and mortality in the population [56]. More recent studies have a prevalence of short stature, underweight, overweight, and obesity among Jordanian school children [57].

1.4.8 Kuwait

Ischemic heart disease was the highest cause of death and disability in Kuwait, and this was followed by low back pain, headache disorders, drug use disorders, neonatal disorders, and road injuries. In line with this, the highest risk factors were high BMI, dietary risks, tobacco use, high fasting plasma glucose, and BP. The finding of ischemic heart disease as the highest cause of disability and high BMI as the greatest risk factor is not surprising given that Kuwait has an adult obesity prevalence rate of 37.9%, which makes it the highest of the Middle East countries listed here (ranked 11th in the world).

1.4.9 Lebanon

The condition which caused the most death and disability in Lebanon was ischemic heart disease, and this was followed by drug use disorders, diabetes, neonatal disorders, headache disorders, and low back pain. The risk factors which drove this were high BMI, tobacco use, high fasting plasma glucose, dietary risks, and high BP. The obesity prevalence rate was high at 32% making it the 18th most obese nation out of the world ranking.

1.4.10 Oman

The highest cause of death and disability in Oman was road injuries. This was followed by ischemic heart disease, neonatal disorders, drug use disorders, headache disorders, and low back pain. However, the greatest risk factors associated with these causes of death and disability were mostly nutrition-based with high BMI at the top of the list, followed by dietary risks, high BP, high fasting plasma glucose, and malnutrition. The adult obesity prevalence rate was lower than most of the Middle East countries at 27%. The fact that road traffic injury was the highest cause of death and disability is consistent with a report from 2013 which showed that the incidence of road crashes in Middle East countries such as Oman has risen dramatically over recent years and is now a leading cause of death for younger adults [58].

1.4.11 Qatar

In Qatar, the greatest causes of death and disability were different than those seen in most other countries. The highest cause was drug use disorders, followed by road injuries, low back pain, headache disorders, diabetes, and depressive disorders. In line with this, the risk factors were also slightly different with high BMI having the highest risk, followed by drug use, high fasting plasma glucose, dietary risks, and occupational risks. The statistic on drug use disorders is most likely linked to the unfortunately high rate of drug and alcohol addiction in this country [59]. The finding that BMI was the highest risk factor is consistent with an adult obesity prevalence rate of 35.1% (equivalent to 15th position in the world obesity prevalence ranking).

1.4.12 Saudi Arabia

The highest causes of death and disability combined in Saudi Arabia were road injuries, ischemic heart disease, headache disorders, low back pain, drug use disorders, and neonatal disorders. Again, these were slightly different from most other Middle East countries and the traffic accident statistic is in line with reports that a car accident happens every minute on average in Saudi Arabia [60]. The greatest associated risks appeared to be linked with diet with high BMI, dietary risks, and high fasting plasma glucose, BP, and low density lipoprotein (LDL) levels. This was correlated with a relatively high adult obesity prevalence rate of 35.4%, which made Saudi Arabia the 14th most obese nation in the world.

1.4.13 Syria

The main causes of death and disability in Syria were similar to those in Iraq. The highest cause was conflict and terror, followed by ischemic heart disease, stroke, low back pain, headache disorders, and neonatal disorders. This is likely to be linked to the ongoing civil war in the country since 2011 [61]. As with most other countries, however, the main risk factors were related to nutrition with dietary risks occupying the top position, followed by high BP, BMI, LDL, and fasting plasma glucose. The obesity prevalence was 27.8% of adults.

1.4.14 Turkey

The highest cause of death and disability combined in turkey was ischemic heart disease, low back pain, neonatal disorders, chronic obstructive pulmonary disease (COPD), stroke, and diabetes. The most causative risk factors were unique to Turkey with tobacco use topping the list, followed by high BMI, high fasting plasma glucose, dietary risks, and air pollution. Although several measures against smoking have been taken over the last decade, smoking still remains a significant burden on health and the economy in Turkey [62]. The finding that the second highest cause of death and disability was high BMI is consistent with an adult obesity rate of 32.1% (17th in the world ranking).

1.4.15 UAE

The highest causes of death in the UAE appeared similar to that seen in Qatar with drug use disorders being the greatest cause, followed by road injuries, ischemic heart disease, low back pain, diabetes, and headache disorders. The main risk factors which drove these causes of death were also similar to those found for Qatar with high BMI, drug use, dietary risks, high fasting plasma glucose, and BP. The obesity rate for adults was 31.7%, which made Qatar the 20th most obese nation.

1.4.16 Yemen

The highest causes of death in Yemen were also slightly different from the other Middle East countries with neonatal disorders, conflict and terror, ischemic heart disease, diarrheal disease, dietary iron deficiency, and congenital defects. These were also driven by somewhat unique risk factors of malnutrition, dietary risks, water, sanitation, and hygiene, high BP, and tobacco use. The ongoing conflict in Yemen has caused the health system to disintegrate, which has left children in particular more vulnerable to malnutrition and disease [63]. Thus, this country has the lowest adult obesity prevalence rate in the Middle East at 17.1%.

1.5 Conclusions and Future Prospects

Recent clinical and experimental studies have shown that the ancient spice turmeric has many beneficial medicinal properties which are thought to be mediated, at least in part, by bioactive curcuminoids. The main properties reported include anti-inflammatory, antioxidant, anti-tumor, anti-aging, and antidiabetic, as well as cardioprotective, hepatoprotective, and neuroprotective activities. The beneficial effects are usually achieved through consumption as part of the diet or as a supplement with other medicines. Currently, one of the most pressing needs is to increase the bioavailability of curcumin to see if the pharmacological effects can be augmented. Thus far, considerable progress has been made toward this objective such as through the development of nano-composite curcumin formulations. Further research on the potential benefits of curcumin is essential considering the alarming rise in age-related diseases such as obesity in the Middle East and the rest of world. Finally, although compelling evidence from the clinical studies has recently emerged to support the efficacy and safety of curcumin supplementation, large-scale event-driven randomized controlled trials are yet to be conducted in order to verify the role of curcumin in the armamentarium of drugs for chronic age-related diseases.

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2 Turmeric and Curcumin: From Traditional to Modern Medicine

Maryam Akaberi, Amirhossein Sahebkar, and Seyed Ahmad Emami

Abstract

The rhizome of turmeric (*Curcuma longa* L.) has been used as an herbal medicine, coloring agent, spice, and food additive for thousands of years in different parts of the world particularly in Asian countries. It has been used for a range of diseases in many traditional medical schools, including Islamic traditional medicine, Chinese traditional medicine, and Ayurveda. It has been used mainly for digestive problems, as a cardio-, hepato-, and neuroprotective agent as well as in many inflammatory conditions such as arthritis and for enhancing immune system. Curcumin, a diarylheptanoid derivative found in turmeric, has anti-inflammatory, antioxidant, and anticancer properties; controls obesity and metabolic problems; and improves memory and mood disorders. Therapeutically, curcumin exhibits promising potential in preclinical and clinical studies and is currently in human trials for a variety of conditions, including metabolic syndrome, nonalcoholic fatty liver disease, rheumatoid arthritis, migraine, premenstrual syndrome, ulcerative colitis, knee osteoarthritis, polycystic ovarian syndrome, atherosclerosis, liver cirrhosis, amyotrophic lateral sclerosis, depression, psoriasis, and Alzheimer's disease. Among all beneficial activities reported for curcumin, the research toward the obesity and metabolic-preventing/suppressing aspects of curcumin is growing. These findings emphasize that most of the traditional applications of turmeric is due to the presence of its key constituent, curcumin. According to the traditional background of turmeric use and clinical values of curcumin, further preclinical studies for unstudied properties and clinical studies with larger sample sizes for confirmed activities are expected.

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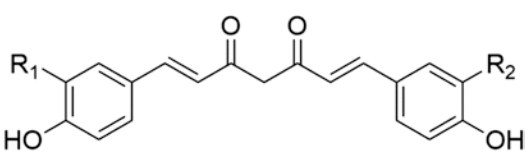
Keywords

Turmeric · *Curcuma longa* · Zingiberaceae · curcumin · traditional medicine · clinical trials · hepato-protective · cardioprotective · neuroprotective

2.1 Introduction

Turmeric, belonging to Zingiberaceae family, is a perennial plant growing up to one meter high with oblong or cylindrical rhizomes. The rhizomes, being externally brown, consists of an egg-shaped primary rhizome called the "tuber" and several branched secondary rhizomes called the "rhizome." The internal color of the rhizomes ranges from yellow to yellow-orange. This yellow color is due to the presence of pigments known as curcuminoids, which possess diverse pharmacological activities [1]. Chemically, curcuminoids known as diarylheptanoids consist of two aryl groups which are connected to each other via a chain with seven carbons. Curcumin (diferuloylmethane) is the most important bioactive curcuminoids. However, there exist other curcuminoids like desmethoxycurcumin and bisdesmethoxycurcumin in turmeric rhizome (Fig. 2.1) [2]. According to preliminary, preclinical, and clinical studies, the yellow pigment curcumin possesses a worthy pharmacology including anti-inflammatory [3, 4], immunomodulatory [5], antioxidant [6], hypolipidaemic [7], antimicrobial [8], anticarcinogenic [9], antitumor [10, 11, 12], radioprotective [13], neuroprotective [14], hepato-protective [15], nephroprotective [16], cardio-protective [17], and vasoprotective activities. Curcumin has been shown to interact with a wide range of biochemical pathways and influence a variety of molecular targets such as cytokines [18], transcription factors [19], kinases [20], growth factors [21], and microRNAs [22].



Curcuminoids:	**R_1**	**R_2**
Curcumin	OCH_3	OCH_3
Desmethoxycurcumin	OCH_3	H
Bisdesmethoxycurcumin	H	H

Fig. 2.1 The chemical structure of the main curcuminoids (the key constituents of turmeric)

Turmeric, also known as Indian saffron, has a long history of use as an herbal medicine, spice, and a coloring agent [23]. The first record of turmeric use dates back to 600 BC in an Assyrian herbal. It was also mentioned by famous Greek physician, Dioscorides, and many traditional scholars in Islamic traditional medicine (ITM) [24–37]. It has also a long-standing reputation in Chinese traditional medicine (TCM), Ayurveda, and different folk medicines around the world [38]. It has been traditionally used for the treatment of a range of diseases including skin disorders (topically) and poor digestion and liver function (internally) [38]. As the knowledge from traditional medicine is a guide for the scientists in the field of natural product–based drug discovery, we decided to investigate the medicinal applications of turmeric in different systems of traditional medicine and the pharmacological activities of curcumin in modern medicine to see the progress from ancient medicine to current clinical trials.

2.2 Traditional View

Turmeric has a long history of medical use in many cultures, particularly in Asia. Turmeric is originally a plant from India and South-East Asia, but nowadays it is cultivated in different regions of the world. However, India is still the largest producer of this valuable plant. Several traditional textbooks [24–37] and electronic scientific literature were searched to find the applications of turmeric in ancient times.

2.2.1 Turmeric in Islamic Traditional Medicine (ITM)

Turmeric, known as Zardchoobeh in Farsi (Persian language) and Hūrd, Kūrkūm, ʿOruqṢūfer, ʿOruqal-ṢabaghinKabir in Arabic, refers to *Curcumalonga* L. [Syn. *C. domestica* Valeton] in ITM textbooks. The latter name has made many of the ITM scientists a bit confused since *Chelidoniummajus* L. is called ʿOruqal-Ṣabaghin Ṣaghir. Some authors do not distinguish between these two names regardless of the suffixes Kabir or Ṣaghir. Even, some scientists believe that ʿOruqal-Ṣabaghin is the name of *Rubiatinctorum* L.

According to turmeric monographs in the most important textbooks of Islamic medicine, it is deduced that most authors consider it as warm and dry in the second degree and others in the third degree. Pharmacologically, different parts of turmeric plants have been prescribed by ITM physicians to manage various health problems particularly, inflammatory-related disorders. For example, the wood of turmeric has been used for the treatment of toothache. Its extract has been applied for eye problems such as cataract and corneal opacity as well as strengthening eyesight. It was administered topically to relieve the aches in the joints. Putting turmeric powder on wet and infectious wounds can dry them out.Topical administration of turmeric is useful for treating scabies, moist scabies, and herpes. In addition, this spice has been highly recommended for obstructive jaundice (caused by bile duct obstruction), cardiac problems like tachycardia, and nervous system–related problems such as epilepsy and paralysis [24–37].

2.2.2 Indian Traditional Medicine (Ayurveda)

Turmeric is commonly called "Haldi" in north India, and "Manjal" in the south [39]. In India, turmeric is used for a range of diseases similar to ITM. Indian people has used turmeric as a gastric tonic, as well as a blood purifier, digestive, antifever, and wound healing agent. It is also used for pregnancy nausea and skin and liver disease. It has been externally used to relieve conjunctivitis, skin infections, arthritis, hemorrhoids, and eczema. In addition, Indian women apply turmeric on their skin to reduce hair growth [39, 40].

2.2.3 Traditional Chinese Medicine (TCM)

In TCM, a range ofapplications have been reported for turmeric rhizome and tuber. Turmeric rhizomes, being a blood and Qi (vital energy) stimulant, have been used as an analgesic, painkiller, and wound healing agent. It has been prescribed for treating jaundice, chest and abdominal pain and swelling, frozen scapula, postpartum abdominal pain, and amenorrhea. Turmeric tuber, known as Yu Jin, is spicy and bitter and has been used in hot conditions like viral hepatitis since it is considered as a cooling agent. Ithas been used to relieve menstrual pain, heal traumatic injuries, treat enlarged liver cirrhosis, and treat mental problems like mania and epilepsy [41].

2.2.4 Traditional Thai Medicine (TTM)

In TTM, turmeric has been used in cases of gastrointestinal ulcers, anal hemorrhoids, vaginal hemorrhoids, skin diseases, ringworms, and insect bites and for the prevention of gonorrhea and common colds [23].

2.3 Clinical View

The biological and pharmacological effects of curcumin have been described by several in vitro and in vivo studies, showing the potential antioxidant, anti-inflammatory, cardio-protective, anti-microbial, nephro-protective, hepatoprotective, hypoglycaemic, immunomodulatory, and anti-rheumatic activities of this valuable compound [37]. Because of potent activities and rare serious side effects of curcumin observed in many preclinical studies, there have been a growing trend in clinical trials on curcumin in the last two decades. A search through scientific databases PubMed and Scopus using the words "curcumin" and "clinical trial" or "trial" yielded a total of 262 articles of which 175 are included in the present paper (Table 2.1). Other articles were systematic reviews, meta-analysis, or irrelevant topics. Similar to in vitro and animal studies, various human trials have shown anti-inflammatory, antioxidant, cardio-protective, antimicrobial properties (especially topically), and tissue protection effects including neuroprotective and hepato-protective activities for curcuminoids (Table 2.1).

Table 2.1 Clinical evidences for biological activities of curcumin

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
1	Analgesic	Postoperative pain after laparoscopic gynecologic surgery	Pilot RCT	60 patients who were to undergo laparoscopic gynecologic surgery	Curcuminoid extract tablets (250 mg) four times a day on postoperative days 1–3 ($n = 30$)	33.1 ± 6.3	↓ Pain severity postoperatively ($p < 0.001$)	[88]
2	Anti-inflammatory	Rheumatoid arthritis (RA)	Double-blind RCT	65 patients with RA	Curcumin nanomicelle capsules (40 mg) 3 times a day for 12 weeks ($n = 30$)	–	Some positive changes in the DAS-28 (disease activity score of 28 joints), TJC (tender joint count), and SJC (swollen joint count), although not significantly	[45]
3	Anti-inflammatory	Migraine	RCT	80 episodic migraine patients	Combination of ω-3 fatty acids (2500 mg) + nano-curcumin (80 mg) over 2 months	–	↓ IL-6 mRNA ↓ hs-CRP serum ($p < 0.05$)	[47]
4	Anti-inflammatory	PMS	RCT	40 women with PMS	Combination of aerobic exercise (for 8 weeks, 3 times in a week) and curcumin capsules (100 mg of curcumin) daily from 7 days before the menstrual period up to 3 first days	18–35	↓ Physical symptoms ($p < 0.05$) ↓ Estrogen levels Improve behavioral and PMS mood symptoms	[89]
5	Anti-inflammatory	Takayasu arteritis (TA)	Double-blind RCT	246 patients with acute TA	Curcumin capsule (300 mg) curcumin daily for 4 weeks	19–52	↓ CRP ↓ TNF-α ↓ ESR (Erythrocyte sedimentation rate) ($p < 0.01$) ↓ BVAS (Birmingham vascular activity score) ($p < 0.05$)	[90]
6	Anti-inflammatory	Mastitisin breastfeeding women	Double-blind RCT	63 breastfeeding women with lactational mastitis	Curcumin topical cream, one pump wvery 8 h for 3 days ($n = 32$)	21–35	↓ Rate of moderate ($p = 0.019$) and mild ($p = 0.002$) mastitis ↓scores for tension ($p < 0.001$), erythema ($p < 0.001$), and pain ($p < 0.001$)	[50]

7	Anti-inflammatory	Radiation dermatitis (RT)	Double-blind RCT	30 breast cancer patients	Curcumin (6 g/d) orally three times per day throughout the course of RT	58.1	↓ Radiation dermatitis severity ($p = 0.008$) ↓ Moist desquamation rate ($p = 0.002$)	[51]
8	Anti-inflammatory	Postmenopausal syndrome	Triple-blind RCT	93 postmenopausal women	Curcumin (500 mg) per day for 8 weeks	51.7	↓ Hot flashes ($p = 0.001$)	[52]
9	Anti-inflammatory	Ulcerative colitis	Double-blind RCT	56 patientswith ulcerative colitis	Curcuminoids nanomicelles (80 mg, three times daily, orally) plus mesalamine (3 g/24 h, orally) for 4 weeks ($n = 28$)	38.2 ± 16.4	↓ Simple clinical colitis activity index	[53]
10	Anti-inflammatory	MeS	Double-blind parallel-group RCT	117 patients with MeS	Curcumin (1 g/day) for 8 weeks ($n = 59$)	44.8 ± 8.7	↓ TNF-α ($p < 0.001$) ↓ IL-6 ($p < 0.001$) ↓ TGF-β ($p < 0.001$) ↓ MCP-1 ($p < 0.001$)	[18]
11	Anti-inflammatory	CPC-SM	Double-blind RCT	89 male subjects	Curcuminoids (500 mg) for 4 weeks ($n = 45$)	51.0 ± 7.3	Improve spirometric parameters FEV1/FVC ($p = 0.002$) ↓ IL-6 ($p < 0.001$) ↓ IL-8 ($p = 0.035$) ↓ TNF-α ($p < 0.001$) ↓ TGF-β ($p < 0.001$) ↓ substance P ($p = 0.016$) ↓ hs-CRP ($p < 0.001$) ↓ CGRP (calcitonin gene-related peptide) ($p < 0.001$) ↓ MCP-1 ($p < 0.001$)	[54]
12	Anti-inflammatory	Obesity	Randomized crossover trial	30 obese individuals	Curcumin (1 g/day) for 4 weeks	18–65	↓ IL-1β ($P = 0.042$) ↓ IL-4 ($P = 0.008$) ↓ VEGF ($P = 0.01$)	[91]
13	Anti-inflammatory	KOA	Pilot double-blind parallel-group RCT	40 patients suffering from knee OA	Curcuminoids (1500 mg/day) for 6 weeks ($n = 19$)	57.3 ± 8.8	↓ WOMAC (Western Ontario and McMaster universities osteoarthritis index) ($p = 0.001$) ↓ VAS ($p < 0.001$) ↓ Lequesne's pain functional index ($p = 0.013$)	[57]

(continued)

Table 2.1 (continued)

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
14	Anti-inflammatory	Solid tumors (ST)	Double-blind RCT	80 subjects with ST	Curcuminoids (180 mg/day) for 8 weeks ($n = 40$)	25–65	↑ QoL ($p < 0.001$) ↓ TNF-α ($p < 0.001$) ↓ TGFβ ($p < 0.001$) ↓ IL-6 ($p = 0.061$) ↓ Substance P ($p = 0.005$) ↓ hs-CRP ($p < 0.001$) ↓ CGRP ($p < 0.001$) ↓ MCP-1 ($p < 0.001$)	[92]
15	Anti-inflammatory	Chronic SM-induced pruritic skin lesions	Double-blind RCT	96 sulfur mustard (SM)-exposed patients	Curcumin (1 g/day) for 4 weeks ($n = 46$)	37–59	↓ IL-8 ($p < 0.001$) ↓ hs-CRP ($p < 0.001$) ↓ CGRP ($p < 0.001$) ↑ QoL	[93]
16	Anti-inflammatory	KOA	Double-blind RCT	44 patients	Diclofenac (75 mg/day) with curcumin (1000 mg/day) for 3 months	–	Decrease pain and improve function in daily living though not significantly	[58]
17	Anti-inflammatory	PMS	Double-blind RCT	70 patients with PMS	Curcumin capsules (100 mg) twice daily for 7 days before menstruation and for 3 days after menstruation for 3 successive cycles ($n = 35$)	25.2 ± 9.2	↓ Total severity of PMS score	[49]
18	Anti-inflammatory, Anti-oxidant	Obesity	Parallel RCT	60 overweight and obese adolescent girls	Curcumin (500 mg/day) + a slight weight loss diet for 10 weeks	13–18	↓ IL-6 ↓TAC (total antioxidant capacity) ↓ MDA ↓ hs-CRP ↓ IL-6	[94]
19	Anti-inflammatory, antioxidant	Infertility in men	Double-blind RCT	60 infertile men	80 mg curcumin nanomicelle daily for 10 weeks ($n = 30$)	20–45	↑ Total sperm count ($p < 0.001$) ↑ Sperm concentration ($p < 0.001$) ↑ Sperm motility ↑ TAC ($p < 0.001$) ↑ MDA ($p < 0.001$) ↑ CRP ↑ TNF-α ($p < 0.01$)	[95]

20	Antioxidant	Polycystic ovarian syndrome (PCOS)	RCT	72 patients with PCOS	Curcumin capsules (1500 mg) 3 times per day for 12 weeks	18–41	↑ Gene expression of PGC1α ($p = 0.011$) ↑ Activity of the Gpx ($p = 0.045$) ↑ Gene expression of SIRT1 ↑ SOD enzymenon-significantly	[61]
21	Antioxidant	β-Thalassemia major	Double-blind RCT	61 patients with β-thalassemia major	Curcumin capsules (500 mg) twice daily for 12 weeks	18–40	↓ Serum MDA ($p = 0.002$), ↓ Total ($p < 0.001$) and direct ($p < 0.001$) bilirubin ↑ TAC ($p = 0.005$)	[96]
22	Antioxidant	CPC-SM	RCT	89 subjects	Curcuminoids (1500 mg/day) in combination with piperine (15 mg/day) for a period of 4 weeks ($n = 45$)	51.0 ± 7.3	↑ Serum GSH, ↓ MDA, Improving COPD assessment test and St. George respiratory questionnaire ($p < 0.001$)	[55]
23	Antioxidant	Type 2 diabetes mellitus (T2DM)	Double-blind RCT	118 patients with T2DM	Curcumin (1000 mg/day) + piperine (10 mg/day) for 8 weeks	18–65	↑ TAC ($p < 0.001$) ↑ SOD activities ($p < 0.001$) ↓ Serum MDA levels ($p < 0.001$)	[97]
24	Antioxidant	KOA	Double-blind RCT	40 patients with KOA	Curcuminoid capsules (1500 mg/day) + piperine (15 mg/day) for 6 weeks ($n = 19$)	57.3 ± 8.8	↑ SOD ($p < 0.001$) ↑ GSH ($p = 0.064$) ↓ MDA ($p = 0.044$)	[98]
25	Antioxidant	CPC-SM	Double-blind RCT	89 patients with CPC-SM	Curcumin (500 mg/day) + piperine (15 mg/day) for 4 weeks ($n = 45$)	51.0 ± 7.3	↑ GSH ↓ MDA Improve COPD assessment test and St. George respiratory questionnaire ($p < 0.001$)	[55]
26	Antioxidant	ST	Double-blind RCT	80 subjects with ST	Curcuminoids (180 mg/day) for 8 weeks ($n = 40$)	25–65	↓ Serum thiobarbituric acid reactive species ($p < 0.001$) ↑ SOD and catalase ↑ GSH ($p < 0.001$) ↑ QoL ($p = 0.003$)	[99]

(continued)

Table 2.1 (continued)

No.	Activity	Health problem	Study design	Participant/sample size	Dosage	Age (years)	Results	Ref.
27	Antioxidant	SM-induced pruritus	Double-blind RCT	96 male Iranian veterans	Curcumin (1 g/day) for 4 weeks ($n = 46$)	37–59	↓ Substance P ($p < 0.001$) ↓ SOD ($p = 0.02$), ↓ Gpx ($p = 0.006$) and catalase ($p < 0.001$) ↓ Pruritus score ($p < 0.001$) ↓ VAS (visual analogue scale) score ($p < 0.001$) ↓ Overall ($p < 0.001$) and objective SCORAD (scoring atopic dermatitis) ($p = 0.009$) ↓ Dermatology life quality index ($p < 0.001$)	[59]
28	Anti-infective	Oral infections	RCT	27 adults	Photodynamic therapy with blue light and curcumin (30 mg/L)	20–35	↓ CFU (colony-forming units) ($p = 0.001$) ↓ Microbial reduction ($p < 0.05$)	[100]
29	Anti-infective	Chronic periodontitis	RCT	10 patients with two sites in the contralateral quadrants having probing pocket depths of ≥5 mm	Curcumin gel tropically+ SRP (scaling and root planning) for 4 weeks	–	↑ Periodontal parameters ↓ Plaque index ↓ Probing depth	[101]
30	Cardio-protective	Metabolic disorders in PCOS subjects	Double-blind RCT	60 women with PCOS	Curcumin (500 mg/day) for 12 weeks ($n = 30$)	18–40	↓ Weight and BMI ($p = 0.03$) ↓ FBG ($p = 0.002$) ↑ Serum insulin ($p = 0.02$) ↑ Insulin resistance ($p = 0.02$) ↑ Insulin sensitivity ($p = 0.02$) ↓ Total cholesterol ($p = 0.001$) ↓ LDL-cholesterol ($p = 0.001$) ↓ TC/HDL-C ($p < 0.001$) ↑ HDL-C levels ($p = 0.01$) ↑ Gene expression of PPAR-γ ($p = 0.03$) ↑ LDL receptor ($p < 0.001$)	[102]