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George E. Barreto
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# Pharmacological Properties of Plant-Derived Natural Products and Implications for Human Health

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# Pharmacological Properties of Plant-Derived Natural Products and Implications for Human Health

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# About the Book

This book *Pharmacological Properties of Plant-Derived Natural Products and Implications for Human Health* presents chapters focused on natural products, in particular medicinal plants and their derived products, as an indispensable source of bioactive molecules that serve as either drug candidates or lead compounds for drug design and discovery purposes. There are several advantages for plant-derived therapeutics, including wide availability, diverse pharmacological actions, and a generally good profile of safety and tolerability. Over the recent years, there have been numerous reports from clinical studies testifying the efficacy and safety of medicinal plants and phytochemicals in ameliorating several human diseases. A plethora of basic studies has also unraveled molecular mechanisms underlying the health benefits of herbal medicines. Nevertheless, issues such as identification of bioactive ingredients, standardization of the products, and drug interactions remain to be further studied. In this book, we compiled 29 chapters on the medicinal properties and pharmacological action of natural products, mainly medicinal plants and phytochemicals, in different settings ranging from *in vitro* models to clinical trials. The goal is to present the reader a comprehensive collection on most of the therapeutic aspects of plant-derived natural products and molecular mechanisms thereof.

Most of the chapters are developed over the use of curcumin as a molecule with antioxidant and anti-inflammatory potential in various pathologies. In the chapter by Alidadi et al., the authors described the effect of curcumin on arterial stiffness, which correlates with lower body weight, and improved pulse wave velocity in patients. Curcumin has also been implicated in regulating long non-coding RNAs (Amini et al.), and modulated inflammatory mechanisms related to lipid metabolism in patients with non-alcoholic fatty liver disease (Mirhafez et al.), and atherosclerosis (Hatamipour et al. and Momtazi-Borojeni et al.). In addition, Naji et al. correlated curcumin with improvement in gastrointestinal cancers, while Shakour et al. highlighted the participation of curcumin in regulating c-reactive protein *in silico*. More interestingly, Zarrinfar et al. described the antifungal effects of curcumin, while Sohrevardi et al. discussed the role of this molecule in women with polycystic ovary, and finally its actions on functional dyspepsia (Panahi et al.). Due to the pandemic, and the search for nutraceuticals that may be able to reduce the symptoms associated with covid-19, Heidari et al. described how curcumin could be considered as a possible therapeutic alternative to drugs currently in use to treat the disease.

Other chapters discussed the pharmacology of plants, their medicinal properties, bioavailability, and metabolism in different tissues, in addition to describing how they can be used to treat different pathologies. In this sense, Ashrafizadeh et al. described the therapeutic properties of ginsenosides on endoplasmic reticulum stress and autophagy, while other authors focused on the effects of plants and their bioactive components on insulin resistance (Mahdavi et al.), plants with anti-addictive potential (Konrath et al.), sleep problems (Lelli et al.), candida albicans (Gharibpour et al.), cannabinoids and cardiovascular system (Liberale et al.), non-alcoholic fatty liver (Simental-Mendía et al.), diabetes and oxidative stress (Yaribeygi et al.), memory and cognitive functions (Yousefani et al), and alopecia (Boghrati et al.), apart from a detailed and insightful discussion on rheum species (Mohtashami et al.), genus rosa (Ayati et al.), Actaea racemosa L. (Salari et al.), Centella asiatica (Torbati et al.), Cichorium (Boghrati et al.), and genus Berberis (Sobhani et al.) plants. Finally, Panahi et al. showed us that magnesium, a molecule highly present in plants, has a protective effect after cerebral ischemia, while Cabezas et al. predicted using *in silico* tools that some bioactive components of plants can regulate fatty acid- binding protein 5 (FABP5), a protein involved in the dysregulation of lipid metabolism.

We hope this comprehensive book is of interest to researchers working in the field and serves as a source of inspiration for future proof-of-concept translational and clinical studies. We would like to acknowledge and thank all the authors for contributing with the presented chapters. Last but not the least, we would like to express our deep appreciation to Mr. Gonzalo Cordova who helped at every step of preparing this collection.

# Contents

# 1 The Effect of Curcumin Supplementation on Pulse Wave Velocity in Patients with Metabolic Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial

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**Abstract**

Cardiovascular disease is a leading cause of death in many societies. Arterial stiffness is an initial sign of structural and functional changes in the arterial wall. Pulse wave velocity (PWV) is the gold standard for non-invasive evaluation of aortic stiffness and a modifiable cardiovascular risk factor. Curcumin is a major component of turmeric with known anti-inflammatory and anti-oxidative effects. Since

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arterial stiffness is affected by inflammation and oxidative stress, it may be improved by curcumin supplementation. The purpose of this clinical trial was to investigate the potential effects of curcumin on improving arterial stiffness in patients with metabolic syndrome. This placebo-controlled, double-blind, randomized clinical trial was conducted among metabolic syndrome patients. Sixty-six eligible individuals were randomly assigned to active intervention or control groups. The active intervention group received curcumin supplement at a dose of 500 mg daily for 12 weeks, whereas the control group received placebo capsule. Physical activity, daily dietary energy intake, anthropometric body composition, and biochemical hemodynamic and arterial stiffness parameters were evaluated at baseline and at the end of the study. Body weight decreased significantly in the curcumin group compared to placebo. Also, curcumin intervention improved PWV, which remained significant after adjustment for potential confounding factors ($p = 0.011$). The current clinical trial demonstrated that daily intake of 500 mg of curcumin for 12 weeks can lead to the improvement of arterial stiffness and weight management among subjects with metabolic syndrome.

**Keywords**

Arterial stiffness · Vascular stiffness · Vascular aging · Arterial aging · Pulse wave velocity · Augmentation index · Curcuminoid · Curcumin · Turmeric · Metabolic syndrome · Obesity

## 1.1 Introduction

Cardiovascular disease (CVD) is the most prevalent cause of death in the world [1]. Arterial stiffness, specifically aortic stiffness, is a primary sign of structural and functional changes in arterial walls and is a predictor of cardiovascular events [2, 3]. Arterial stiffness explains the reduced ability of an artery in dilation and constriction in response to pressure alterations [4]. Collagen and elastin are two important proteins in the arterial wall and any imbalance between them, such as caused by inflammation or increased luminal pressure, results in increased collagen, reduced elastin and subsequently enhanced stiffness of arterial wall [5, 6].

Various methods, both invasive and noninvasive, have been accepted to assess arterial resilience. Pulse wave velocity (PWV) and wave reflection are two noninvasive methodologies for vascular stiffness assessment [7, 8]. Augmentation pressure (AP) and augmentation index (AIX) are measures of pulse wave reflection and evaluated using the pulse wave analysis (PWA) technique [9]. Large elastic artery stiffness and systemic arterial stiffness are evaluated through aortic PWV and wave reflection, respectively [10]. Aortic PWV, as the 'gold-standard' measurement of arterial stiffness, has been determined by carotid-femoral PWV (cf-PWV) [2, 11]. Also, AIX can demonstrate the CVD risks independently of peripheral pressures, as shown in a recent meta-analysis [12].

Several situations can reduce vascular elasticity such as aging, central obesity, smoking, diabetes, hypertension, inflammation disease, metabolic syndrome and genetic factors [8, 13]. Metabolic syndrome is one of the major causes of CVD, and has been described as one of the main public health global challenges [14, 15]. According to the International Diabetes Federation (IDF) definition, metabolic syndrome can be diagnosed with central obesity and the existence of two or more other clinical features that include elevated blood pressure, increased levels of triglyceride and fasting plasma glucose, and reduced HDL-cholesterol concentrations [16, 17]. Lifestyle modifications, such as improved dietary habits, can have a favorable effect on vascular stiffness [18]. Turmeric is a source of an orange-yellow pigment polyphenolic compound called curcumin [1,7-bis-(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione] [19]. Curcumin has been reported to have many beneficial effects on health [20–28]. It has been shown that curcumin can

induce nitric oxide production and reduce oxidative stress and inflammation in animal and in vitro models of vascular-related disorders [29–32]. A recent preclinical study in young and older male mice showed that 4 weeks of curcumin supplementation resulted in improved endothelial function and arterial stiffness by enhancement of nitric oxide bioavailability and reduced oxidative stress [33].

The purpose of this study was to test the hypothesis that 12 weeks of curcumin supplementation would lead to improved arterial stiffness indices in metabolic syndrome patients.

## 1.2 Methods

This randomized, double-blinded, placebo-controlled clinical trial with parallel design was conducted at the Persian cohort center of Imam Reza hospital, Mashhad, Iran. In this trial, 200 new cases of metabolic syndrome were assessed using inclusion and exclusion criteria. Of these cases, 66 individuals aged 30–60 years met the IDF criteria [17] and were incorporated into this 12 week study (Fig. 1.1). Exclusion criteria were the following: pregnancy; lactation; smoking; drug abuse; use of statins, contraceptive pills, analgesic, antidiabetic, antiplatelet, or anti-inflammatory drugs; consumption of antioxidants, multivitamins, multivitamin-mineral or herbal supplements 3 months before starting the study; and a history of diabetes, kidney failure, cancer, gallstones, calcium oxalate stones, autoimmune, biliary or obstructive diseases.

This investigation was approved by the Ethics Committee of Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran (serial no. IR.MUMS.MEDICAL.REC.1397.452), in accordance with the Declaration of Helsinki. In addition, this study was registered on Iranian Registry of Clinical Trials website (clinical trial registration no. IRCT20180619040151N2). At the beginning of the study, the nature, side effects, and advantages of the study were illustrated to volunteers and their written informed consent was obtained. All measurements were done at the Persian cohort center of Imam Reza hospital after 12 h fasting (water allowed) and > 24 h refrainment from physical activity.

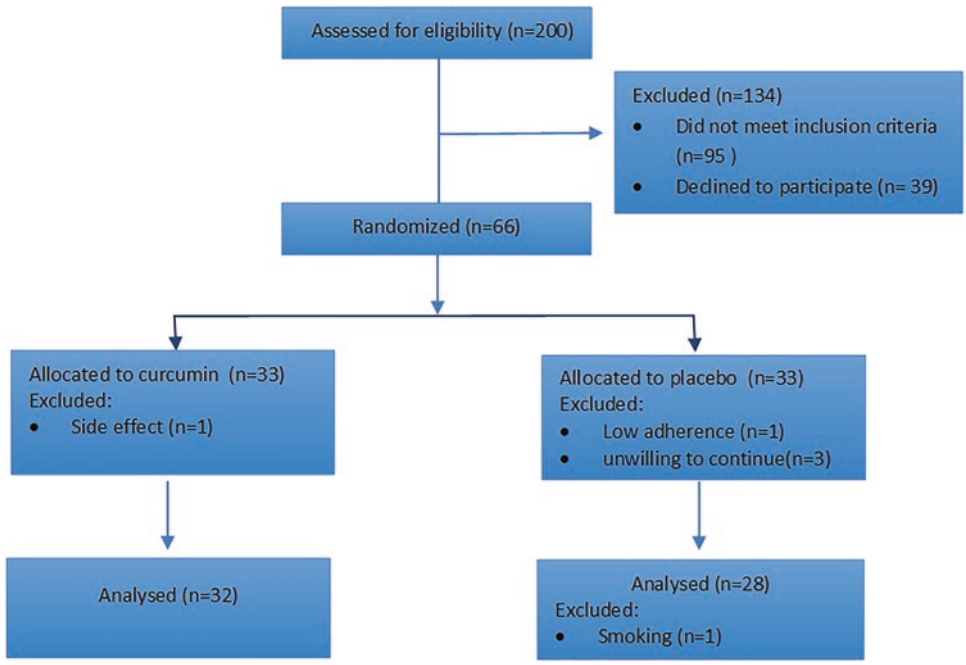


**Fig. 1.1** Flow diagram of study

### 1.2.1 Randomization Procedure

After conducting the screening and consent steps, the randomization procedure was performed using a stratified permuted block scheme, in which the stratification was based on age and gender. Subsequently, all participants were randomly allocated to either the curcumin or the placebo group.

### 1.2.2 Interventions

Curcumin [500 mg (95% total curcuminoids), provided by Karen Pharma and Food Supplement Company] or placebo capsules [500 mg of lactose, provided by the Faculty of Pharmacy, Mashhad University of Medical Sciences] were taken by the participants once per day with the midday meal. Every four weeks during the trial, in-person check-in visits were implemented to change the intervention capsules and evaluate participant compliance by survey and pill count. Additionally, tolerability and side effects of the interventions were assessed during these check-in visits.

### 1.2.3 Dietary and Physical Activity Assessment

Average daily dietary energy intake was evaluated by two-day dietary recall at baseline and at week 12. Dietary recall data were analyzed by Nutritionist IV software (N-Squared Computing, Salem, OR, USA). Also Physical activity was estimated by the long version of International Physical Activity Questionnaire (IPAQ) at baseline and week 12.

### 1.2.4 Anthropometric and Body Composition Assessment

Anthropometric and body composition measures were taken with subjects wearing light-weight clothing with no shoes on. Standing height was measured to the nearest 0.5 cm using a wall-mounted stadiometer. Waist, hip, wrist and neck circumferences were determined by a tension-gated tape at baseline and week 12. Waist circumference was measured to the nearest 0.5 cm at the midway of the distance between the lower rib margin and the iliac crest at the end of a gentle expiration and in the direction of the horizontal plane. Hip circumference was measured to the nearest 0.5 cm around the widest portion of the gluteal area in standing position [34]. Wrist circumference (WrC) was measured around the bony prominences of the radial and ulnar styloids [35]. Neck circumference (NC) was measured at the midpoint of the neck or just below the laryngeal prominence (‘Adam’s apple’) ‘in men with an obvious Adams apple, while the tape was placed vertically [34]. WrC and NC measures were taken to the nearest 0.1 cm. Also, weight and body composition parameters were determined via a bioelectrical impedance body composition analyzer (InBody 770, Biospace Co., Ltd. Seoul, South Korea). To decrease examiner-related errors, all the measurements executed by the same person.

### 1.2.5 Laboratory Parameters

Blood samples were collected from the antecubital vein after 12 h overnight fasting at baseline (0 weeks) and at the end of 12 weeks intervention. Serum concentrations of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using the BT1500 chemistry analyser (Biotecnica Instruments S.p.A., Rome, Italy).

### 1.2.6 Blood Pressure and Arterial Stiffness Measurements

Brachial and aortic blood pressure, aortic pulse pressure (PP), mean arterial pressure (MAP,) heart rate (HR), AIX, AIX75, AP, and arterial age measurements were obtained after the participants had rested in a supine posture for at least 10 min in a calm, thermoneutral room. Measurements were obtained with the SphygmoCor XCEL System

(Sphygmocor; AtCor Medical, Sydney, Australia) by a trained physician. After PWA, cf-PWV was measured for assessment of aortic stiffness using the SphygmoCor XCEL System.

### 1.2.7 Statistical Analyses

The sample size was statistically calculated to achieve a power of 90 according to change in AIX75 in the Sugawara [36] investigation. Statistical analysis was performed using SPSS 16. Assessment of data normality was performed using the One-Sample Kolmogorov-Smirnov test. In addition, histogram plots were evaluated visually, and it was observed that data distribution for normality was acceptable. Finally, linear regression was used to confirm the final results.

## 1.3 Results

A total of 66 metabolic syndrome patients were initially enrolled in the study but five placebo group participants (one smoking, three unwilling to continue, one adherence less than 80%) and one curcumin group participant (reflux side effect) did not complete the study (Fig. 1.1). The baseline characteristics of the final 60 study participants, who were randomly assigned into the two treatment arms, are shown in Table 1.1. None of the participant characteristics were significantly different between the two groups at base-

**Table 1.1** Subject characteristics in curcumin and placebo intervention

| | Curcumin | | Placebo | |
|---|---|---|---|---|
| Variables | Week 0 | Week 12 | Week 0 | Week 12 |
| Sex[a] | | | | |
| Male (%) | 43.8 | – | 53.6 | – |
| Female (%) | 56.2 | | 46.4 | |
| Age (year) | 42.84 ± 6.25 | – | 44.43 ± 5.92 | – |
| Physical activity [b] (MET/min/wk) | 826.5(300–1829) | 573(316–1267) | 688.5(352–1160) | 495(233–1449) |
| Energy intake (kcal/day) | 2120.36 ± 501.91 | 2042.02 ± 549.22 | 2057.4 ± 583.15 | 2172.43 ± 575.44 |
| Weight (kg) | 80.09 ± 9.67 | 79.55 ± 9.71 | 79.34 ± 12.39 | 79.77 ± 12.81 |
| Waist circumference (cm) | 97.15 ± 7.46 | 96.25 ± 8.06 | 100.13 ± 11.46 | 100.16 ± 11.86 |
| Neck circumference (cm) | 37.63 ± 2.67 | 37.55 ± 2.67 | 38.3 ± 3.84 | 38.45 ± 3.88 |
| Waist to hip ratio | 0.89 ± 0.05[c] | 0.89 ± 0.05 | 0.94 ± 0.07 | 0.94 ± 0.07* |
| Waist to height ratio | 0.58 ± 0.05 | 0.57 ± 0.05 | 0.6 ± 0.06 | 0.6 ± 0.07 |
| Body mass index ($kg/m^2$) | 28.87 ± 3.65 | 28.7 ± 3.86 | 29.16 ± 4.06 | 29.3 ± 4.06 |
| A body shape index ($m^{11/6}\ kg^{-2/3}$) | 0.08 ± 0.003[c] | 0.079 ± 0.004 | 0.082 ± 0.004 | 0.082 ± 0.004* |
| Protein (kg) | 9.94 ± 1.71 | 9.98 ± 1.71 | 10.02 ± 1.96 | 10.11 ± 2.07 |
| Skeletal muscle mass (kg) | 28.06 ± 5.13 | 28.08 ± 5.16 | 28.26 ± 5.94 | 28.48 ± 6.27 |
| Fat mass (kg) | 36.68 ± 8.21 | 36.22 ± 8.55 | 35.9 ± 6.35 | 35.87 ± 6.74 |
| Visceral fat area($cm^2$) | 143.72 ± 45.23 | 140.7 ± 47.04 | 135.18 ± 37.43 | 135.41 ± 39.1 |
| FPG (mg/dl) | 101.13 ± 10.96 | 94.28 ± 12.8** | 99.04 ± 12.64 | 96.28 ± 17.25 |
| TC(mg/dl) | 180.56 ± 39.01 | 175.22 ± 41.93 | 181.71 ± 37.57 | 178.79 ± 42.92 |
| TG (mg/dl) | 163.25 ± 52.45 | 148.97 ± 59.87 | 189.46 ± 87.21 | 164.11 ± 77.01 |
| HDL-C (mg/dl) | 46.13 ± 10.66 | 44.16 ± 9.62 | 44.11 ± 8.82 | 43.89 ± 9.79 |
| LDL-C (mg/dl) | 101.79 ± 29.56 | 102.42 ± 32.28 | 99.71 ± 31.41 | 102.07 ± 35.89 |
| AST (U/l) | 22.25 ± 9.36 | 18.22 ± 9.73** | 22.57 ± 7.9 | 19.54 ± 8.68** |
| ALT (U/l) | 28.84 ± 13.69 | 23.69 ± 12.59** | 28.18 ± 13.91 | 24.54 ± 13.46** |

Values are means±SD. *FPG* fasting plasma glucose, *TC* total cholesterol, *TG* triglyceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

*$P < 0.05$, between groups after 12 weeks of intervention

**$P < 0.05$, compared to baseline

[a]Chi-square

[b]Mann- Whitney test, values are medians ± interquartile range

[c] $P < 0.05$, compared to placebo at baseline

line (all $P > 0.5$), except for waist to hip (WHR) ratio and A Body Shape Index (ABSI), which were both higher in the control group ($P < 0.05$). In the current study, energy intake and physical activity did not change in either the curcumin and placebo groups compared to baseline.

### 1.3.1 The Effect of Curcumin on and Anthropometric, Body Composition, and Serological Tests

The effects of curcumin supplementation on anthropometric, body composition and biochemical tests are presented in Table 1.1 and Table 1.2. After 12 weeks of intervention, a statistically significant reduction in mean body weight was observed in the curcumin compared to the placebo group but body composition and other anthropometric parameters showed no significant changes. A decreasing trend was observed in anthropometric and body composition parameters, including waist circumference, neck circumference, body mass index (BMI), and visceral fat area after curcumin treatment relative to placebo. In both groups, liver enzymea (ALT and AST) were decreased significantly but there was no significant difference between the groups.

### 1.3.2 The Effect of Curcumin on Arterial stiffness and Hemodynamic Parameters

Table 1.3 indicates that there was no difference between the groups in vascular stiffness and hemodynamic parameters at the baseline of the study. As shown in Table 1.4, a significant reduction in PWV was observed following 12 weeks of curcumin intervention compared to placebo. Also, it was shown that after adjusting for confounding factors including age, gender, change in physical activity and energy intake by regression, the curcumin treatment significantly reduced aortic PWV, relative to placebo (Table 1.5). Finally, brachial and aortic systolic blood pressure (SBP) was reduced but totally hemodynamic parameters were not significantly improved with curcumin consumption compared to placebo.

**Table 1.2** Changes in anthropometric, body composition parameters, and serological tests during the intervention

| Variables | Curcumin | Placebo | P- value* |
|---|---|---|---|
| Weight (kg) | −0.53 ± 2.07 | 0.42 ± 1.5 | 0.04 |
| Waist circumference (cm) | −0.9 ± 2.51 | 0.02 ± 2.15 | 0.13 |
| Neck circumference (cm) | −0.07 ± 0.54 | 0.15 ± 0.64 | 0.14 |
| Waist to hip ratio | −0.003 ± 0.01 | −0.0007 ± 0.01 | 0.62 |
| Waist to height ratio | −0.005 ± 0.01 | 0.0005 ± 0.01 | 0.11 |
| Body mass index (kg/m$^2$) | −0.17 ± 0.75 | 0.13 ± 0.52 | 0.07 |
| A body shape index (m$^{11/6}$ kg$^{-2/3}$) | −0.0004 ± 0.001 | −0.0003 ± 0.001 | 0.72 |
| Protein (kg) | 0.03 ± 0.18 | 0.08 ± 0.33 | 0.49 |
| Skeletal muscle mass (kg) | 0.01 ± 0.5 | 0.21 ± 0.9 | 0.29 |
| Fat mass (kg) | −0.45 ± 1.77 | −0.02 ± 1.84 | 0.36 |
| Visceral fat area(cm$^2$) | −3.01 ± 12.39 | 0.23 ± 10.67 | 0.28 |
| FPG (mg/dl) | −6.84 ± 14.08 | −2.82 ± 33.53 | 0.29 |
| TC(mg/dl) | −5.34 ± 23.41 | −2.92 ± 6.33 | 0.74 |
| TG (mg/dl) | −14.28 ± 43.41 | −25.35 ± 65.66 | 0.43 |
| HDL-C (mg/dl) | −3.12 ± 6.11 | −0.21 ± 8.81 | 0.13 |
| LDL-C (mg/dl) | 0.63 ± 17.9 | 2.35 ± 29.08 | 0.78 |
| AST (U/l) | −4.03 ± 5.08 | −3.03 ± 6.51 | 0.5 |
| ALT (U/l) | −5.15 ± 7.26 | −3.64 ± 7.63 | 0.43 |

Values are means±SD
*Between groups

**Table 1.3** Cardiovascular parameters before and after intervention

| | Curcumin | | Placebo | |
|---|---|---|---|---|
| Variables | Week 0 | Week 12 | Week 0 | Week 12 |
| Aortic SBP (mmHg) | 108.44 ± 9.05 | 105.97 ± 7.22* | 109.36 ± 10.65 | 108.11 ± 11.25 |
| Aortic DBP (mmHg) | 74.5 ± 7.04 | 73.44 ± 5.66 | 76.57 ± 8.25 | 76.18 ± 10.22 |
| Aortic PP (mmHg) | 33.94 ± 5.29 | 32.53 ± 5.22 | 32.79 ± 5.1 | 31.93 ± 3.99 |
| Aortic MAP (mmHg) | 88 ± 8.23 | 86.47 ± 6.05 | 70.18 ± 7.66 | 69 ± 6.6 |
| HR (beats /min) | 69.69 ± 9.28 | 68.31 ± 5.64 | 70.18 ± 7.66 | 69 ± 6.6 |
| Aortic AP | 9.91 ± 5.14 | 9.78 ± 4.64 | 9.29 ± 3.75 | 8.86 ± 3.07 |
| Aortic AIX | 28.25 ± 11.75 | 29.38 ± 11.71 | 27.79 ± 9.35 | 27.32 ± 7.5 |
| Aortic AIX75 | 25.75 ± 12.68 | 26.19 ± 12.16 | 25.54 ± 9.98 | 24.36 ± 7.73 |
| Brachial SBP (mmHg) | 118.13 ± 9.54 | 114 ± 53 ± 7.83* | 118.75 ± 12.01 | 117.11 ± 12.23 |
| Brachial DBP (mmHg) | 73.75 ± 6.91 | 72.63 ± 5.71 | 75.86 ± 7.82 | 75.5 ± 9.92 |
| Arterial age(year) | 52.59 ± 18.82 | 51.53 ± 17.3 | 51.89 ± 16.45 | 48.54 ± 11.35 |
| Cf-PWV(m/s) | 7.60 ± 1.43 | 6.67 ± 0.97** | 7.43 ± 1.74 | 7.11 ± 2.03 |

Values are means±SD. SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, MAP: mean arterial pressure, HR: heart rate, AP; augmentation pressure, AIX; augmentation index, AIX75; augmentation index normalized to a HR of 75 bpm, cf-PWV; carotid to femoral pulse wave velocity

*$P < 0.05$, compared to baseline

**$P < 0.001$, compared to baseline

**Table 1.4** Differences of Cardiovascular parameters during the intervention

| Variables | Curcumin | Placebo | P-value* |
|---|---|---|---|
| Aortic SBP (mmHg) | −2.46 ± 6.81 | −1.25 ± 6.94 | 0.49 |
| Aortic DBP (mmHg) | −1.06 ± 6.04 | −0.30 ± 5.92 | 0.66 |
| Aortic PP (mmHg) | −1.4 ± 4.99 | −0.85 ± 4.36 | 0.65 |
| Aortic MAP (mmHg) | −1.53 ± 6.23 | −0.85 ± 6.24 | 0.67 |
| HR (beats /min) | −1.37 ± 9.07 | −1.17 ± 8 | 0.93 |
| Aortic AP | −0.12 ± 4.29 | −0.42 ± 3.24 | 0.76 |
| Aortic AIX | 1.12 ± 9.34 | −0.46 ± 7.2 | 0.46 |
| Aortic AIX75 | 0.43 ± 9.83 | −1.17 ± 7.89 | 0.49 |
| Brachial SBP (mmHg) | −3.59 ± 6.96 | −1.64 ± 7.69 | 0.3 |
| Brachial DBP (mmHg) | −1.12 ± 6 | −0.35 ± 5.78 | 0.61 |
| Arterial age(year) | −1.06 ± 18.31 | −3.35 ± 14.62 | 0.59 |
| Cf-PWV(m/s) | −1.09 ± 0.83 | −0.43 ± 1.24 | 0.03 |

Values are means±SD

*Between groups

**Table 1.5** Linear regression to adjust for confounding factors on PWV change

| Variables | B | Std. error | Beta | P value |
|---|---|---|---|---|
| Δ energy intake | −0.001 | 0.001 | −0.314 | 0.053 |
| Δ physical activity | 0.00006 | 0.00007 | 0.119 | 0.431 |
| Group | 0.84 | 0.319 | 0.39 | 0.011 |
| Gender | 0.547 | 0.307 | 0.251 | 0.082 |
| Age | 0.018 | 0.026 | 0.098 | 0.484 |

Δ after – before

## 1.4 Discussion

The present investigation demonstrated that 12 weeks of regular ingestion of curcumin supplement ameliorated aortic stiffness in metabolic syndrome patients. We assessed PWV as a principal marker of large arteries stiffness and observed that curcumin supplementation significantly reduced PWV. Analysis of potential sex differences did not show any significant improvement in arterial stiffness parameters in women who received curcumin intervention. Initial evidence in a preclinical study performed by Fleenor et al. [33] demonstrated that dietary curcumin supplementation improves age-related large elastic artery stiffness by nitric oxide bioavailability restoration, oxidative stress reduction and normalization of collagen I and advanced glycation end products (AGES) deposition in the arterial wall.

This finding is consistent with research showing that arterial stiffness (PWV or carotid arterial compliance) significantly improves after several weeks to months of curcumin treatment [20, 37, 38]. However, two studies reported that curcumin ingestion does not affect PWV [36, 39]. A recent study conducted by Campbell et al. demonstrated that only subjects with a higher baseline value of aortic PWV (arterial stiffness) responded to curcumin supplementation. In the present investigation, the mean age of patients receiving curcumin was 44 years old and the mean baseline cf-PWV value was 7.6 m/s. However, the mean cf-PWV for healthy 40–49 year-old subjects was found to be 7.2 m/s [40]. This suggests that there may be differences in the measured mean baseline cf-PWV across different studies.

We found that the reflection wave indices (aortic AP, AIX, and AIX75) were not affected by the curcumin intervention. In agreement with this finding, Sugawara et al. [36] found that curcumin significantly decreased aortic AIX75 only when combined with exercise training. AIX is a complicated variable that shows the stiffness of smaller muscular arteries as well as microvascular density, number and location of terminal arterioles that give rise to reflected waves, the velocity of the pressure wave, and the pattern of left ventricular ejection. In addition, in contrast to PWV, AIX is influenced by gender and anthropometric measurements [41].

Today lifestyle modification is the main strategy for prevention of CVD, and weight management is a key factor in this objective. For this objective, curcumin has been reported to have beneficial effects on obesity management [42–45]. A preclinical study suggested that curcumin has antiobesity effects through downregulating the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer binding protein α, which are key transcription factors in adipogenesis and lipogenesis [46]. This results in suppression of adipocyte differentiation, fatty acid esterification, and adipokine-induced angiogenesis in adipose tissue, and induction of fatty acid oxidation and increased apoptosis of adipocytes. In humans, 10 weeks of curcumin supplementation significantly decreased mean body weight in overweight type 2 diabetes patients [42]. consistent with this finding, we observed that 12 weeks of curcumin ingestion significantly decreased body weight compared to the placebo group. Although not statistically significant, the curcumin intervention also tended to decrease WC, NC, BMI, and visceral fat area, while these parameters had an increasing trend in the placebo group.

Metabolic syndrome is a serious health condition of impaired glucose tolerance and, consequently, elevation of fasting plasma glucose is one of its criteria. Many animal studies have demonstrated that curcumin anti-inflammatory and antioxidant activities may be responsible, at least in part, for its anti-hyperglycemic effects [47–49]. Studies in humans have been inconsistent as some have confirmed the curcumin anti-hyperglycemic effect [42, 43, 50], and others have found no effect [51, 52]. In our study, FPG did not significantly change with curcumin supplementation compared to placebo. Also, we did not observe any significant changes in lipid profiles between the groups. Many preclinical studies have found that curcumin reduces serum cholesterol levels via upregulating the expression of hepatic LDL receptors, inhibition of LDL oxidation, enhancement of cholesterol excretion by increasing bile acid secretion, and suppressing

the expression of genes involved in cholesterol biosynthesis [53, 54]. Furthermore, a recent animal study showed that curcumin reduced serum TG concentrations through inhibition of sterol regulatory element-binding protein 1 (SREBP-1c), liver X receptor alpha (LXR-α), and the target lipogenic enzymes fatty acid synthase and acetyl CoA carboxylase [55]. To our knowledge and according to literature review, curcumin should be consumed in higher doses or in a higher efficacy form (nano-formulation or in combination with an adjuvant) to influence FPG and lipid profiles.

Since the liver is the main organ for drug metabolism and elimination, it should be considered that hepatotoxic reactions may take place there in the present study. Such drug-induced hepatotoxicity manifestations are various, ranging from a mild elevation of liver enzymes to fatal hepatic failure [56]. During the present clinical trial, liver function was not affected by the interventions, as determined by the lack of effect on ALT and AST, which are commonly used as biomarkers of liver damage.

This study was limited by its short-term duration of follow-up that precluded the possibility of assessing hard cardiovascular endpoints. Furthermore, although the mean baseline cf-PWV values of participants were modestly elevated, not all participants had high PWV. The inability to present a mechanistic view for the beneficial effects of curcumin on vascular aging was another limitation of this study.

## 1.5 Conclusions

In the present study, we observed the favorable effects of 12 weeks of curcumin supplementation on arterial stiffness and weight control. We also demonstrated that curcumin intake for 12 weeks was well tolerated. Further trials are warranted to confirm the present findings in target populations with elevated arterial stiffness.

**Conflict of Interest** None of the authors had declarations of interest to publish.

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# 2 Role of Curcumin in Regulating Long Noncoding RNA Expression in Cancer

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**Abstract**

Phytochemicals are various compounds produced by plants. There is growing evidence on their potential health effects. Some of these compounds are considered as traditional medicines and used as painkillers, anti-inflammatory agents, and for other applications. One of these phytochemicals is curumin, a natural polyphenol derived from the turmeric plant (*Curcuma longa* L.). Curcumin is widely used as a food coloring, preservative and condiment. It has also been shown to have antioxidative and anti-inflammatory effects. Moreover, there is growing evidence that curcumin alters long noncoding RNAs (lncRNAs) in many kinds of cancer. These noncoding RNAs can cause epigenetic modulation in the expression of several genes. This study reviews reports of curcumin effects on lncRNAs in lung, prostate, colorectal, breast, pancreatic, renal, gastric, and ovarian cancers.

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**Keywords**

Cancer · Curcumin · Non-coding RNA · lncRNA · Epigenetic · Cancer · Therapeutics

## 2.1 Introduction

Cancer is one of the major human illnesses resulting in considerable mortality. The rate of morbidity due to cancer has been increased in recent years [1–4]. Chemotherapy is considered as one of the major therapeutic approaches for management of cancer by inducing apoptosis and inhibiting tumor growth [5–8]. However, chemotherapy affects both healthy and cancer cells resulting in considerable side effects [9]. Hence, there has been an increasing use of therapies which target cancer cells more specifically. Various methods of targeted therapies include monoclonal antibodies [10], small molecule inhibitors [11], immunotoxins [12], and the use of drug nanocarriers to deliver the chemotherapeutic agents to selected cancer cells [13–15]. Other therapeutic options for cancer treatment include various radiotherapies [16] and hormonal treatments [17–20].

Along with these standard methods of cancer treatment, a number of natural products [21–24], have been considered which target diverse signaling pathways in cancer cells [5, 25, 26]. These natural compounds are called phytochemicals and can be divided as as polyphenols, carotenoids, terpenoids, alkaloids, phytosterols, and lectins, to name a few The polyphenols are one of the most abundant secondary metabolites in plants with antioxidant protperties. One example of the polyphenol class which has received considerable attention is curcumin [(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione], which is yellow pigmented polyphenol from the rhizome of *Curcuma longa* Linn with several health benefits (Fig. 2.1) [27–30]. Several studies have demonstrated the safety, pharmacological activity and possible therapeutic use of curcumin in the treatment of various diseases [31–45].

It has been shown that curcumin decreases the rapid growth of distinct cancer cells via inhibition of migration, growth and invasion. Additionally, curcumin can induce apoptosis and repress cancer cell development and progression, both in-vivo and in-vitro. One mechanism on how this is achieved occurs through noncoding

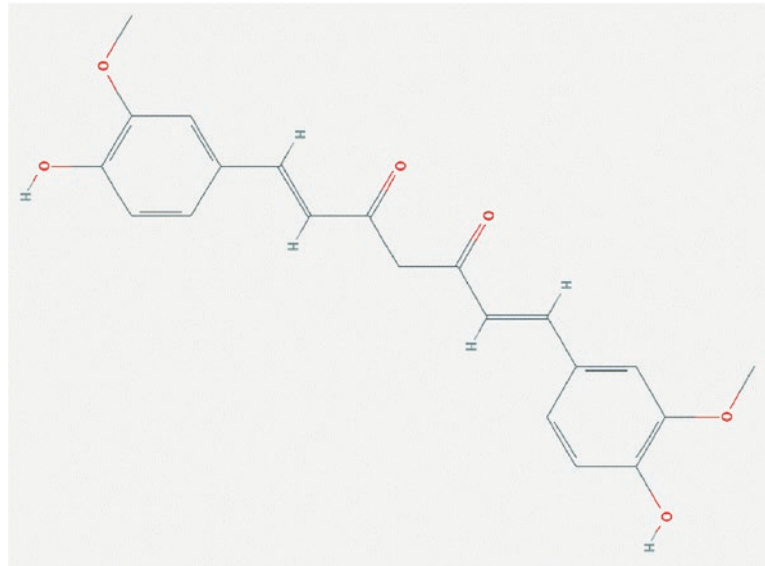

**Fig. 2.1** 2D structure of curcumin (PubChem CID: 969516)

RNA molecules, which regulate gene expression at the epigenetic level via complementary base-pairing with sequences within mRNA molecules. Curcumin has been shown exert epigenetic regulatory effects on noncoding RNAs in different types of cancers [46, 47]. Noncoding RNAs could be categorized as long noncoding (lnc) and short noncoding (snc) RNAs, based on length [48, 49]. Here, we review the effects of curumin on lncRNAs as a potential therapeutic approach in cancer treatment.

## 2.2 The Role of lncRNAs in the Development of Cancer

lncRNAs or long noncoding RNAs are noncoding sequences of ribonucleotides which are generally longer than 200 nucleotides without an open reading frame, and they are not translated into proteins. These lncRNAs are responsible for the expression of various genes associated with the development of diseases such as cancer [50]. These noncoding RNAs interact with RNA, DNA, and protein complexes, thereby, acting as chromatin organization, transcriptional, and post-transcriptional regulators. In the case of cancer, this could result in altered expression of genes associated with cell growth, metastasis, and tumor formation [51]. Many phytochemicals such as curcumin, can modulate lncRNAs and thereby dysregulate these processes in cancer [52].

There are three possible mechanisms by which lncRNAs are involved in cancer development and progression: i) translational regulation; ii) post-translational control; and iii) chromatin remodeling (Fig. 2.2). For example, HOTAIR is a lncRNA that upregulates the c-myc proto-oncogene in breast and ovarian cancer, which in turn could be down-regulated by curcumin at the transcriptional level [53, 54]. The influence of lncRNA regulation on chromatin remodeling occurs via effects on chromatin remodeling enzymes, which alters chromatin structure and thereby changes susceptibility to genetic reprogramming mechanisms.

## 2.3 Biogenesis and Function of lncRNAs

It is commonly recognized that lncRNAs are by-products of transcription and usually consist of more than 200 bases [55]. This occurs mostly through the actions of RNA polymerases II and III [49, 56]. Similar to the microRNAs (miRNAs), lncRNAs have the capability of binding to specific proteins, RNA, as well as nucleating RNA compartments, which generate the ribonucleoprotein complexes. It should be noted that lncRNAs could operate directly following their synthesis, and function as scaffolds for promoting dynamic gene control [57]. In this way, lncRNAs can have both normal and pathological functions [48]. In cancer, the expression of thousands of lncRNAs can vary based on the kind of tumor [49, 58]. Most of the well-studied lncRNAs play a crucial role in controlling critical cellular processes such as growth and apoptosis to maintain homeostasis while others take part in cancer development via promoting uncontrolled cell proliferation, metastasis, inducing genetic instability, developing drug resistance and invasion capacity [59].

Two studies registered 7258 sncRNAs and 15,767 annotated lncRNAs in the GENCODE database, consisting of the greatest popular compilation of transcripts [48, 60]. Based on the outcomes of the tissue microarray analyses and next-generation sequencing, it is understood that gene expression can be modulated by the lncRNAs at various stages, including epigenetic, transcriptional and post-transcriptional levels. Therefore, lncRNAs have considerable scope as drug targets in diverse medical areas [61]. Notably, lncRNAs may function as a molecular decoy or sponge of miRNAs, which influences miRNA activity and the level of expression [62]. Likewise, lncRNAs directly or indirectly target the miRNAs. However, an active crosstalk has been observed between miRNAs and lncRNAs via a double-negative feedback circle [58]. Ye et al. demonstrated an example of such cooperation between micoRNAs and lncRNAs which results in the development of cancer [63]. In this study, 5 miRNA nodes, 13 lncRNA nodes, and 45

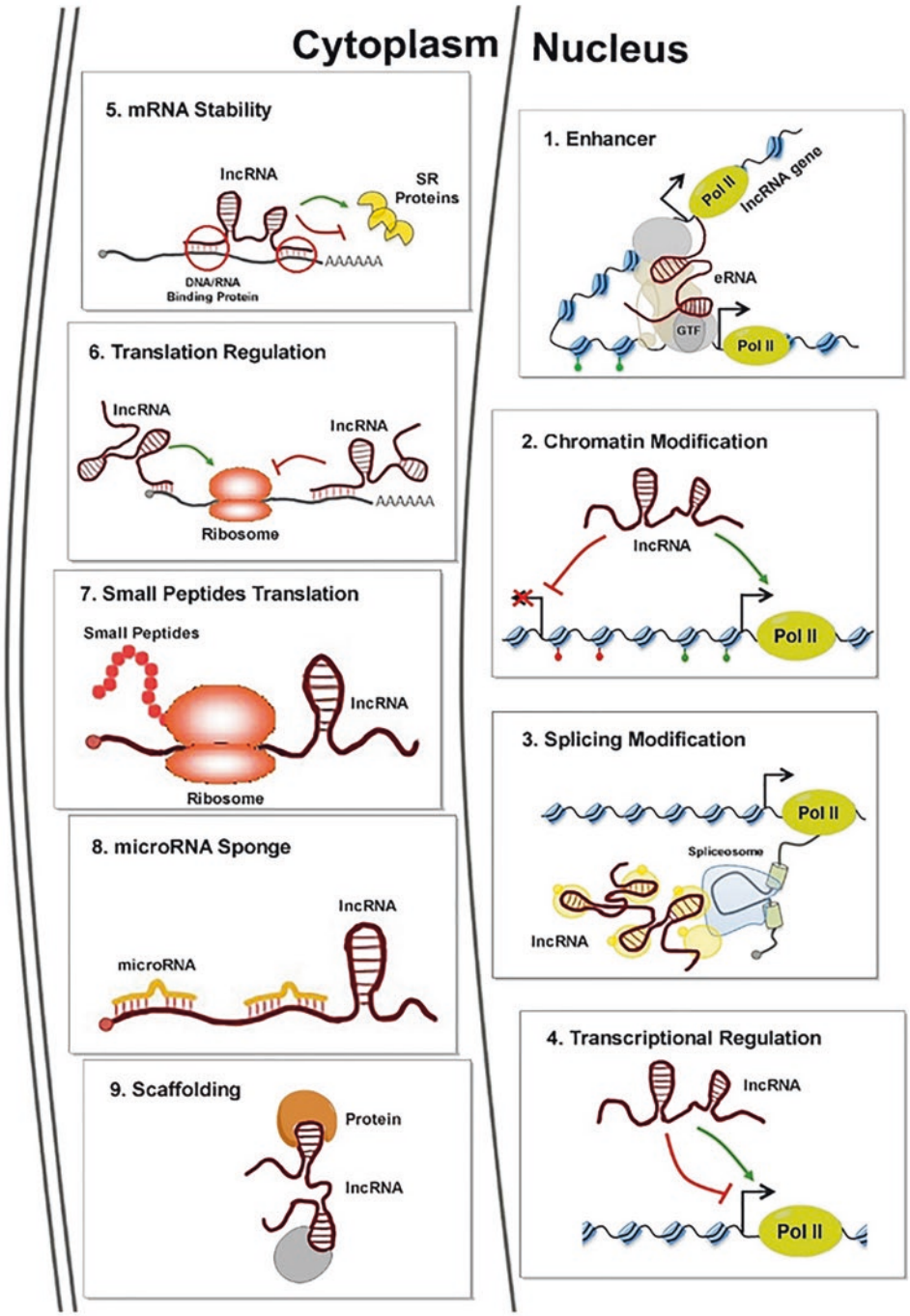


**Fig. 2.2** Long non-coding RNAs' (lncRNAs) main mechanisms of action. 1: enhancing DNA transcription, 2: employing chromatin-modifying complexes (e.g. histone methylases, acetylases, and deacetylases) to target sites in the genome, 3: regulating pre-mRNA splicing, 4: binding to transcription factors and changing their function, 5: binding to mRNAs to increase stability and regulate trafficking, 6: binding to mRNAs to induce translation activation or suppression, 7: some lncRNAs encode biological small peptides, 8: competing with the regulatory activity of miRNAs, 9: LncRNAs can alter protein function by scaffolding roles and providing docking site in the same biological pathway

mRNA nodes participate in phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) signaling pathway regulation and dysregulation of important oncogenes related to prostate cancer. In this role, the lncRNAs contribute to the epigenetic, post-transcriptional, and transcriptional modulation of gene expression. Moreover, two primary groups of lncRNAs have been reported with either oncogene [e.g., metastasis-associated lung adenocarcinoma transcript 1(MALAT1), SOX2 overlapping transcript (SOX2-OT), HOX transcript antisense RNA (HOTAIR) and H19], or tumor suppressor [e.g., maternally expressed 3 (MEG3), taurine upregulated gene 1 (TUG1), growth arrest specific 5 (GAS5), and promoter of CDKN1A antisense DNA damage-activated RNA (PANDAR)] roles, based on the respective pathological characteristics [64].

## 2.4 Effects of Curcumin on lncRNA Expression in Cancer

The following sections highlight examples in which the ability of curcumin treatment to alter lncRNA expression is tested in various cancers.

### 2.4.1 Colorectal Cancer (CRC)

Evidence suggests the contribution of lncRNAs in the metastasis, invasion, chemotherapy and radiotherapy resistance in CRC via interaction with distinct signaling pathways like Wnt, epithelial to mesenchymal transition (EMT), transforming growth factor-β (TGF-β), and miRNAs [65]. In particular, many studies have shown the ability of lncRNAs for direct regulation of the metastatic paths in CRC. As a result, 28 CRC-associated oncogene lncRNAs (including UCA1, HOTAIR, MEG3 and H19) have been recognized in one of the studies and 13 tumor suppressor lncRNAs (such as GAS5 and MEG3) have found in the other [66].

However, in-vitro experiments showed that curcumin treatment led to increased lncRNA PANDAR in CRC cells and this attenuated senescence and increased apoptosis [67]. In addition, silencing PANDAR in curcumin treated cells enhanced the apoptosis rate potentially by an increased level of p53 upregulated modulator of apoptosis (PUMA). Curcumin increases the expression of the neighbor of BRCA1 gene NBR2 lncRNA, which inhibits proliferation, clone formation, and decreases the percentage of S-phase cells in colorectal cancer via the 5′ AMP-activated protein kinase (AMPK) pathway [68]. Plasmacytoma variant translocation 1 (PVT1) is another lncRNA which is also expressed in colorectal cancer and its effects on tumor formation, expansion, and drug resistance are well-established. The finding that curcumin prevents PVT1 over-expression in tumor cells [69] adds further weight to the idea that it may be considered as a potential novel adjuvant treatment in CRC.

### 2.4.2 Pancreatic Cancer

We identified increased expression levels of H19, lncRNAs, regulator of reprogramming (ROR), nuclear-enriched abundant transcript-1 (NEAT1), MIR31 host gene, and nuclear transport factor 2 pseudogene 3 (NUTF2P3) in pancreatic cancer using various systems [70]. Another study reported curcuminn treatment in BxPC3-GemR pancreatic ductal adenocarcinoma cells augmented reversal of gemcitabine resistance via suppression of the expression of the polycomb repressive complex 2 (PRC2) subunit, enhancer of zeste homolog-2 (EZH2), and the respective lncRNA, PVT1 [69] (Table 2.1).

### 2.4.3 Lung Cancer

A study by Wang et al. showed that curcumin induces apoptosis in A549 lung cancer cells by down-regulation of urothelial cancer associated-1 (UCA1) lncRNA [72]. This occurs via suppression of Wnt and mTOR pathways. Curcumin has also been found to regulate other lncRNAs which influence oncogene expressions in lung cancer. Another study has shown that there are multiple

**Table 2.1** Alterations of long noncoding RNAs in cancer in response to curcumin

| Cancer type | lncRNA* | Cell line | References |
|---|---|---|---|
| Colorectal | PANDAR (UP)<br>NBR2 (UP)<br>PVT1 (DOWN) | CRC | [67, 68] |
| Pancreatic | ROR, H19, NEAT1 (UP)<br>Nuclear-enriched abundant transcript-1 (NEAT1) (UP)<br>MIR31HG (UP)<br>Nuclear transport factor 2 pseudogene 3 (NUTF2P3) (UP)<br>PVT1(DOWN) | BxPC3-GemR | [70–72] |
| Lung | Urothelial cancer associated-1 (UCA1) (DOWN)<br>GAS5, PANDAR, MEG3 (DOWN)<br>HOTAIR, MALAT1, H19 (UP)<br>PVT1(DOWN) | A549 | [72–78] |
| Breast | MALAT1, HOTAIR, H19<br>GAS5 (DOWN)<br>Tusc7, ATB (DOWN) | MDA-MB231, SKBR3, and MCF7 | [76–78] |
| Ovarian | MEG3 (UP) | A2780cp | [80] |
| Prostate | HOTAIR, SOCS2-AS1, PVT1<br>MEG3, GAS5, and H19<br>ROR<br>CCAT1 (DOWN) | CRPC<br>HuPCaSCs<br>PC3-TXR /DU145-TXR | [5, 23, 82–85] |
| Renal | HOTAIR (DOWN) | 769-P, 769-P-vector, 769-P-HOTAIR, 786–0, and Kert-3 | [86, 87] |
| | XIST (DOWN) | ACHN and Caki-2 | |
| Hepatocellular | MEG3 (UP) | HepG2 and HuH-7 | [88] |
| Gastric | H19 (DOWN) | SGC-7901 | [89] |
| Nasopharyngeal | GUCY2GP (UP)<br>H2BFXP (UP)<br>LINC00623 (UP)<br>ZRANB2-AS2 (DOWN)<br>LOC100506835 (DOWN)<br>FLJ36000 (DOWN) | CNE-2 | [90] |

dysregulated lncRNAs in non-small cell lung cancer (NSCLC), which are potential candidates for new biomarkers are drug targets [73]. They found downregulation of 9 lncRNAs (e.g., GAS5, PANDAR, MEG3) and upregulation of 24 lncRNAs (e.g., HOTAIR, MALAT1, H19) in NSCLC. The PVT1 lncRNA contributes to a number of cancers including NSCLC. This lncRNA promotes lung cancer cell proliferation, invasion, metastasis, and drug resistance. The molecular process underlying its effects appears to involve interaction with the c-Myc oncogene, modulation of miRNAs, and regulation of gene transcription and protein expression. In addition, over-expression of the PVT1 gene has been observed in patients suffering from NSCLC [74, 75]. Since curcumin has been found to downregulate the expression of this lncRNA, further studies should assess its utility as a novel treatment approach in lung cancer.

### 2.4.4 Breast Cancer

In the case of breast cancer, the association of multiple lncRNAs (e.g., MALAT1, HOTAIR, H19) has been described [76]. In addition, a study showed that treatment of MDA-MB231, SKBR3 and MCF7 breast cancer cells with dendrosomal curcuminin (DNC) led to increased expression of

growth arrest-specific 5 (GAS5) and tumor suppressor candidate 7 (Tusc7) lncRNAs [77]. Conversely, down-regulation of GAS5 decreased the anti-cancer effects of the DNC treatment. The activated by TGF-β (ATB) lncRNA is overexpressed in breast cancer cells and exacerbates the metastasis of these cells via the ROR pathway. Interestingly, curcumin treatment suppresses this effect, again supporting its potential use as a breast cancer treatment [78].

### 2.4.5 Ovarian Cancer

A meta-analysis has identified lncRNA clusters with distinctive metastatic capacities in ovarian cancer cells [79]. One of these, lncRNAs, maternally expressed 3 (MEG3), is known to be decreased in ovarian cancer. This is important as another study showed that curcumin was able to suppress resistance of ovarian cancer cells to the chemotherapeutic cisplatin via a change in gene methylation leading to reduction of miR-214 and restoration of MEG3 levels [80].

### 2.4.6 Prostate Cancer

Prostate cancer antigen-3 (PCA3) was one of the first highly up-regulated lncRNAs to be indentified for prostate cancer and it appears to be specific for this form of cancer [81]. Seventeen lncRNAs (HOTAIR, SOCS2-AS1, PVT1, & so on) were found to be involved in the progression of prostate cancer. Further, lower expression level of three lncRNAs (MEG3, GAS5, & H19) was also found in prostate cancer [82]. In-vitro, studies in pancreatic cancer cell line (HuPCaSCs) revealed an overexpression of miR-145, cell cycle arrest, suppression of the cell rapid growth, and invasion following pre-treatment with curcumin. Consequently, luciferase activity assays reflected that lncRNA-ROR and Oct4 could relatively attach to the miRNAs as a result of the respective popular binding sites of miR-145. Altogether, downregulating the endogenous lncRNA-ROR increases the expression level of miR-145 in HuPCaSC and thus miR-145 suppresses the rapid cell proliferation via the declined level of Oct4 expression [5, 80, 83]. In a research conducted in the year 2020, CCAT1 or colon cancer-associated transcript 1 found in colon cancer has a decisive role in the progression of prostate cancer as well as reducing the sensitivity to paclitaxel (PTX) a chemotherapeutic agent in prostate cancer. The expression of this lncRNA is accompanied by microRNA-24-3p (miR-24-3p) and fascin1 (FSCN1) synthesis in malignant cells. Curcumin is found to reduce the level of CCAT1 and inactive PI3K/Akt/mTOR pathways [84, 85].

### 2.4.7 Renal Cancer

During renal cell carcinoma (RCC), kidney cancer cells originate from proximal convoluted tubule. According to Pei et al., a direct correlation exists between HOTAIR mRNA expression and cell migration and metastasis of renal cancer cells. In the mentioned study, curcumin dose-dependently inhibited cell migration [86]. Another lncRNA called XIST (x inactive specific protein) plays a pivotal role in renal cell carcinoma progression. The underlying molecular mechanism is still unclear. However, documents show the possibility of the interaction between miR-106b-5p and increased expression of P21. Curcumin regulates XIST/miR-106b-5p/P21 axis in RCC cells [87].

### 2.4.8 Hepatocellular Cancer

Hepatocellular carcinoma is a prevalent type of cancer that is associated with high rates of chemotherapy resistance. On the other hand, MEG3 is a common tumor suppresser lncRNA expressed in healthy cells. This lncRNA is downregulated in hepatocarcinoma cells, and the reason underlies the specific methylation pattern of MEG3 promoter by DNMT1, DNMT3A and 3B. Curcumin overexpresses MEG3 *via* downregulating DNMT1, DNMT3A and 3B, thereby altering methylation process and assisting in hepatocellular cancer treatment [88].

### 2.4.9 Gastric Cancer

Long noncoding RNA H19 is overexpressed in gastric cancer cells and can directly inhibit p53 expression, thereby promoting gastric cancer progression. Turmeric extract has been reported to reduce overexpression of H19 and protect against gastric cancer [89].

### 2.4.10 Curcumin in Nasopharyngeal Cancer

In nasopharyngeal CNE-2 carcinoma cells, curcumin was found to radiosensitize the cells. Moreover, curcumin significantly up-regulated the expression of lncRNAs such as GUCY2GP, H2BFXP, and LINC00623, while the expression of ZRANB2-AS2, LOC100506835, and FLJ36000 were down-regulated [90]. In another study, curcumin modulated the lncRNAs such as AF086415, AK056098, AK095147, AK294004, MUDENG, and RP1-179 N16.3, thereby radiosensitizing these cells [91].

## 2.5 Conclusions and Perspectives

Noncoding RNAs contributes to the regulation of the biology of cancer cells so that these RNAs could be recognized as the promising approaches to the management of various cancers. The ability of curcumin to modulate lncRNA expression has provided a new molecular basis for its biological activities Moreover, it has been found that natural products such as curcumin and other plant derivatives would apply considerable antiproliferative impacts on different types of cancer cells. Inhibiting the proliferation of the cancer cells via regulation of specific noncoding RNAs by phytochemicals could be a potential turning point in cancer treatment. Thus, it could be concluded that the above results would help elucidate the mechanisms underpinning the effectiveness of phytochemicals, which would present worthwhile insight into the assessment of the novel cancer treatments. However, most of these studies have been carried out in cell culture models. Future studies should also elucidate if curcumin can effectively regulate lncRNA expression in human subjects.

**Competing Interests** Muhammed Majeed is the founder of Sabinsa Corporation and Sami Labs Ltd. The authors have no other conflicting interests to disclose.

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