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Review Article

Clinical Application of "Curcumin", a Multi-Functional Substance

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Abstract

Throughout the world, societies have used both tradition and science to identify foods that can prevent and treat various diseases. In recent years, remarkable progress has been made in the pharmacological activation and clinical application of functional food-derived substances. In this review article, we focus on the functional food-derived substance curcumin, a primary component of natural turmeric (Zingiberaceae). Despite its range of reported pharmacological effects, including anti-oxidant, anti-inflammatory, and anti-tumor ones, curcumin is limited in its clinical applicability by its low bioavailability during oral administration. We therefore developed a highly absorbable curcumin formulation (THERACURMIN®) using nanoparticulation and surface processing techniques. Subsequent studies in humans have shown that THERACURMIN® is highly absorbable and mitigates liver dysfunction. Our translational research indicated curcumin's potential as a therapy for heart failure by the compound's inhibitory effect on histone acetylation of p300 in cardiomyocyte nuclei. Our clinical findings from a pharmacokinetic study showed curcumin's potential for treating pancreatic cancer by inhibiting NF-κB activity. Finally, we showed combining aerobic exercise and curcumin improved arterial stiffness. These studies demonstrate that THERACURMIN® has improved bioavailability and, based on the pharmacology of curcumin, a number of beneficial effects. Further studies of THERACURMIN® and curcumin-related compounds are expected for their wider clinical application.

KEY WORDS: Curcumin, DDS, Heart failure, Cancer, Arterial stiffness

1. Curcumin

The Japanese population is an aging one, with respective life expectancies of 79.64 and 86.39 years in men and women as of fiscal year 2010, ranking fourth and first in the world, respectively. Consequently, more and more attention is being focused on the new academic discipline of Anti-Aging Medicine, which aims to slow age-related pathological changes. One important research subset in this field involves foods and herbs known to be particularly effective in maintaining and enhancing health. Given that these foods of interest have been shown to have remarkable pharmacological effects, comparable to those of existing pharmaceutical products, substantial research efforts are underway to elucidate the active compounds responsible for these positive effects.

One such food substance being examined is curcumin, a polyphenol found in turmeric at a content of 3% to 5% [1]. Traditionally, it has been used as spice and colorant in Indian curries, as well as a component of Chinese medicines, and has been approved as a safe food in the US, where it is used in mustard, yellow pickled radish, and other confectioneries along with foods such as curry in Japan.

In recent years, a number of studies across the globe have investigated the various biological effects of curcumin [1,2]. In addition to its reported cytoprotective effect, curcumin is known to exert an antioxidant effect by removing free radicals and an anti-inflammatory effect by inhibiting the activation of NF-κB [2]. Two clinical trials investigating curcumin have concluded that the compound may be useful in preventing heart failure and effective against a range of diseases, including cancer and Alzheimer's disease (***Fig. 1***) [2,3].

In the present article, we review the recent topics on curcumin including development of a highly absorbale formulation, mode of action, and clinical applications.

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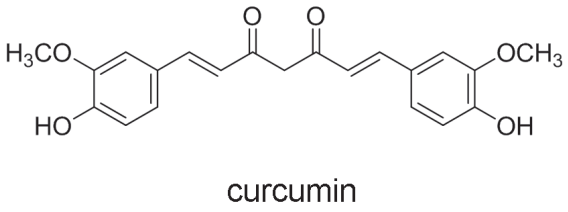

curcumin

B

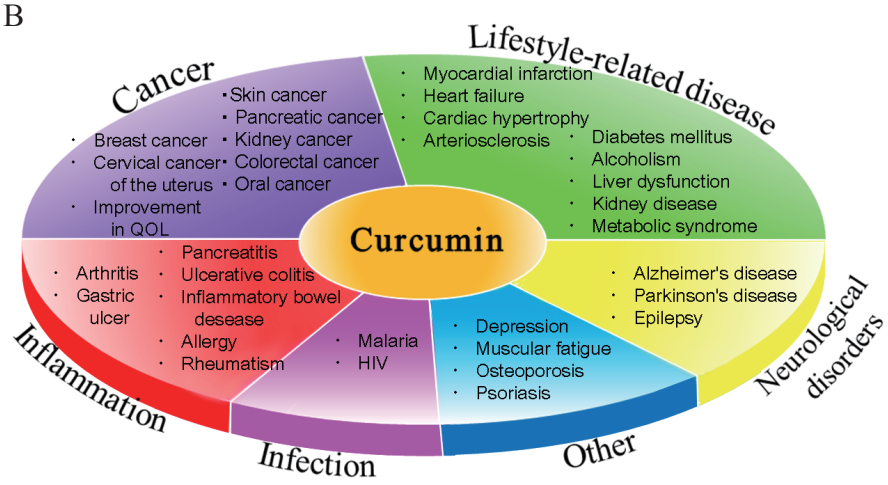

Fig. 1. **Structure and therapeutic application of curcumin**
A: Chemical structure of curcumin
B: Various diseases against which curcumin may have therapeutic effects [check]

2. Development and clinical application of THERACURMIN®

Curcumin (***Fig. 1A***) is highly lipophilic, and its poor bioavailability after oral administration has been the major challenge limiting the clinical application of curcumin [1]. We therefore used nanoparticulation and surface processing techniques to develop THERACURMIN® (THERAVALUES CORPORATION, Chiyoda-ku, Tokyo, Japan), a highly absorbable curcumin formulation that is easily and stably dispersible in water [4]. In this section, clinical studies that have been conducted in humans to evaluate the health effects of THERACURMIN® on alcohol metabolism [4], liver function, and the skin are reviewed.

I) Development of THERACURMIN®

Among a number of attempts that have been made to improve absorption of curcumin, THERACURMIN® has shown one of the most promising results.

Studies investigating the absorption of THERACURMIN® in rats and humans after oral administration [4] found that the blood curcumin concentration increased dose-dependently in both species, while the area under the blood concentration-time curve (AUC) was more than 30-fold higher in rats and more than 27-fold higher in humans compared to that of curcumin bulk powder. Given such a high absorbability, clinical studies of THERACURMIN® to evaluate health benefits were initiated.

II) Improvement in liver function by THERACURMIN®

We conducted a crossover study to evaluate the effects on liver function after oral administration of THERACURMIN® that contains 30 mg of curcumin 30 minutes before alcohol intake (n = 7) [4]. The alcohol-related increase in blood acetaldehyde concentration was significantly reduced when THERACURMIN® was received compared to the time when subjects did not take THERACURMIN®.

In another study, THERACURMIN® was orally administrated to healthy volunteers (n = 19), including those with relatively high values for liver function markers such as gamma-glutamyl transpeptidase (γ-GTP), aspartate transaminase (AST) , and alanine transaminase (ALT), at a dose of 90 mg twice daily in the morning and evening for 1 month, with little lifestyle modification. Significant decreases were observed in overall mean AST (−12%, p = 0.016), ALT (−16%, p = 0.041), and γ-GTP (−15%, p = 0.010). Further, liver function was more markedly improved in subjects who had higher baseline values than in relatively normal ones.

While curcumin has long been believed to benefit the liver, its exact mechanism of action is poorly understood. The findings that THERACURMIN® reduced the alcohol-related increase in blood acetaldehyde concentration and normalized liver function markers will be helpful in clarifying how curcumin can be therapeutic to the liver.

III) Inhibition of skin damage by THERACURMIN®

Exposure of the skin to ultraviolet radiation induces NF-κB activation and promotes inflammation, resulting in abnormal keratinization, pigmentation associated with proliferation of melanocytes, and collagen degradation in the skin (***Fig. 2***) [5]. Curcumin has been reported to exert not only an antioxidant effect, but also anti-inflammatory effect by inhibiting NF-κB activation followed by inhibition of the expression of collagen degrading enzymes, and is thus expected to have an inhibitory effect on the progression of skin damage.

To further examine such properties, we evaluated the efficacy of THERACURMIN® in improving skin damage in an ultraviolet irradiation-induced pigmentation model of brown guinea pigs. In animals that received THERACURMIN® by gavage at daily doses of 1 and 10 mg/kg as curcumin for 4 weeks, pigmentation was inhibited by 6% to 18% based on skin brightness at the site of ultraviolet irradiation compared to that of the control group.

In healthy women who received THERACURMIN® at doses of 30 and 90 mg as curcumin twice daily in the morning and evening for 4 weeks, the skin moisture level significantly increased from baseline (average 15% increase). In addition, dose-dependent improvement was observed based on findings via diagnostic imaging of spots, wrinkles, and pores on the facial skin.

In summary, THERACURMIN® reduced skin pigmentation and maintained skin moisture.

IV) Potential Health Benefits of THERACURMIN®

Recent basic research has shown that one of the critical curcumin's mechanism of actions is the inhibition of NF-κB activation. Thus, in addition to the effects on the liver and skin described above, THERACURMIN® is also expected to be effective against a number of conditions related with chronic inflammation, including cancer, heart failure, dementia, exercise-related muscular fatigue, and arthritis. Its high absorbability also suggests that the THERACURMIN® can maximize the potential biological effects expected with curcumin. Several clinical studies investigating these potential effects are currently underway.

3. New molecular-targeted heart failure therapy using THERACURMIN®

In recent years, Japan has seen a rise in the number of patients suffering from hypertension and arteriosclerosis due to lifestyle changes, subsequently resulting in a surge in the incidence of hypertensive heart disease, myocardial infarction, and the final stages of heart failure. Given Japan's aging population, which is already at increased risk of such illnesses, these numbers are expected to continue to rise, putting great economic and social strain on the country. As such, methods for preventing and treating heart failure have therefore received a great deal of attention, and we describe curcumin as one potential candidate in the present section [6].

I) Search for a molecular target

Several studies have reported that expression of a number of genes is affected on development of heart failure. Effectively treating this disease therefore requires identification of common nuclear pathways for therapeutic targeting. In our own studies, we identified cardiac-specific GATA transcription factors as a potential target for such pathways during cardiomyocyte hypertrophy [7-11]. Subsequently, we considered whether or not the activity of histone acetyltransferases (HATs) plays an important role in the development of heart failure, as excessive nuclear acetylation can be observed in left ventricular cardiomyocytes after the onset of myocardial infarction. We found that both p300, a transcriptional coactivator with HAT activity, and GATA transcription factors (p300/GATA pathway) play a primary role in gene expression regulation leading to heart failure [12-14]. More specifically, overexpression of p300 in cardiomyocytes induced cardiomyocyte hypertrophy depending on HAT activity, whereas a p300 mutant completely lacking HAT activity showed no such hypertrophy [15].

In addition, we bred a strain of mice overexpressing p300 in the heart which subsequently developed cardiac hypertrophy and experienced heart failure [8]. During this development, acetylation of not only histone but also the cardiac-specific transcription factor GATA4 increased, indicating that the hypertrophic response gene was more likely to bind to the promoter. Further, cardiac remodeling was markedly increased after the onset of myocardial infarction. However, in mice

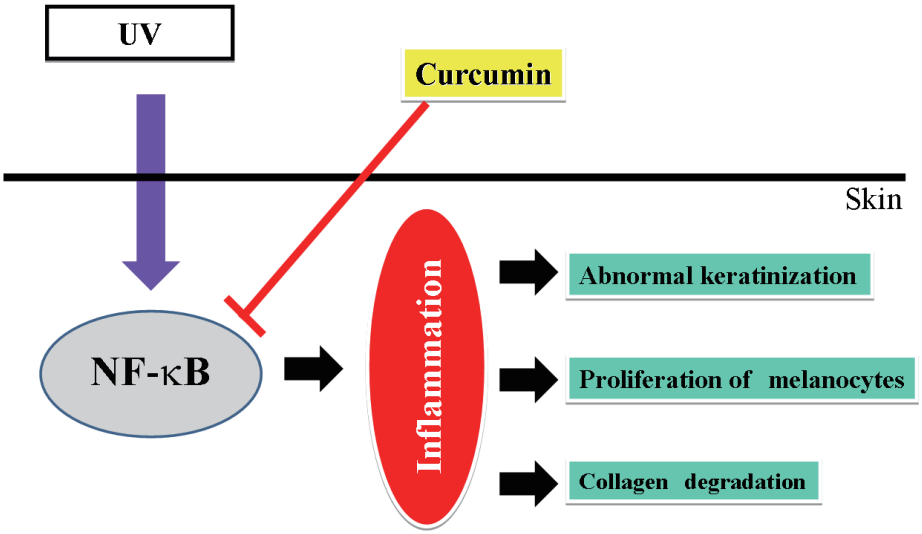

Fig. 2. **Ultraviolet rays may affect the skin through NF-κB-induced inflammation.**

overexpressing the p300 mutant lacking HAT activity in the heart, the increase in remodeling was similar to that seen in wild-type mice [15]. These data suggest that p300 HAT activity is a potential target for heart failure therapy.

Given recent findings that curcumin is a specific inhibitor of p300 HAT activity [16], we investigated whether or not this inexpensive, natural compound with an established safety profile could be used in heart failure therapy.

II) New molecular-targeted therapeutic agent for heart failure: curcumin (Fig. 3)

Prior to animal studies, the effects of curcumin were evaluated in cultured primary cardiomyocytes from neonatal rats [17]. On treatment of these cells with the α1-adrenergic receptor agonist phenylephrine, curcumin inhibited phenylephrine-induced increases in the transcription activity of promoters for hypertrophic response genes ANF and β-MHC, thereby inhibiting cardiomyocyte hypertrophy, as well as phenylephrine-induced increases in the acetylation of the cardiac-specific transcription factor GATA4, the binding of GATA4 to p300 and DNA, and nuclear and histone acetylation. Curcumin also inhibited p300-induced increases in transcription activity for hypertrophic response genes as well as cardiomyocyte hypertrophy. These results show that curcumin inhibits cardiomyocyte hypertrophy by inhibiting p300 HAT activity.

Following the above *in vitro* studies, we investigated curcumin's inhibitory effect on the progression of heart failure in two different rat models of heart failure [17]. Salt-sensitive Dahl rats, a model of hypertensive heart failure, were orally administered curcumin at 50 mg/kg/day for 7 weeks during the transition from compensatory hypertrophy to heart failure (from 11 to 18 weeks of age). Findings on echocardiography showed that curcumin significantly improved left ventricular fractional shortening (FS), an index for cardiac contractility. Curcumin also inhibited left ventricular wall thickening and hypertrophy of cardiomyocytes, as well as increases in p300 protein levels, GATA4 acetylation, and binding of GATA4 to p300 in the heart.

A similar study was conducted in a rat model of myocardial infarction to confirm these effects in other models of heart failure. Curcumin or a control was orally administered daily for 6 weeks, starting 1 week after the generation of myocardial infarction. Similarly to our findings in Dahl rats described above, curcumin diminished systolic dysfunction and inhibited myocardial infarction-induced cardiomyocyte hypertrophy.

However, despite the above-described promising findings of curcumin inhibiting cardiomyocyte hypertrophy in cultured cardiomyocytes as well as the development of heart failure in rat models of hypertensive heart disease and myocardial infarct, both common causes of heart failure, curcumin's capability of inhibiting the development of cardiac hypertrophy characterized by preserved systolic function and decreased diastolic function at earlier stages of hypertension remained unknown. In a subsequent study, salt-sensitive Dahl rats fed a high-salt diet from age 6 weeks developed marked hypertension which progressed cardiac hypertrophy with conserved systolic function and diastolic dysfunction by age 11 weeks. To evaluate the effect of curcumin on the development of cardiac hypertrophy, econd group of Dahl rats which were on a high-salt diet were orally administered curcumin for 5 weeks, starting at age 6 weeks. Curcumin significantly inhibited the increase in left ventricular posterior wall thickness associated with high-salt-diet-induced hypertension. In addition, inhibition of cardiomyocyte hypertrophy was histologically confirmed. Taken together, these findings demonstrated that curcumin inhibits not only the development and aggravation of hypertensive heart failure (systolic dysfunction) but also the formation of hypertensive cardiac hypertrophy (diastolic dysfunction). In the hypertension model, curcumin directly acted on cardiomyocytes to inhibit hypertrophy without lowering blood pressure, indicating that its mechanism of action importantly differs from that of antihypertensive agents (β-blockers, ARBs, ACE inhibitors). As such, curcumin may be more useful in treating cardiac hypertrophy and heart failure

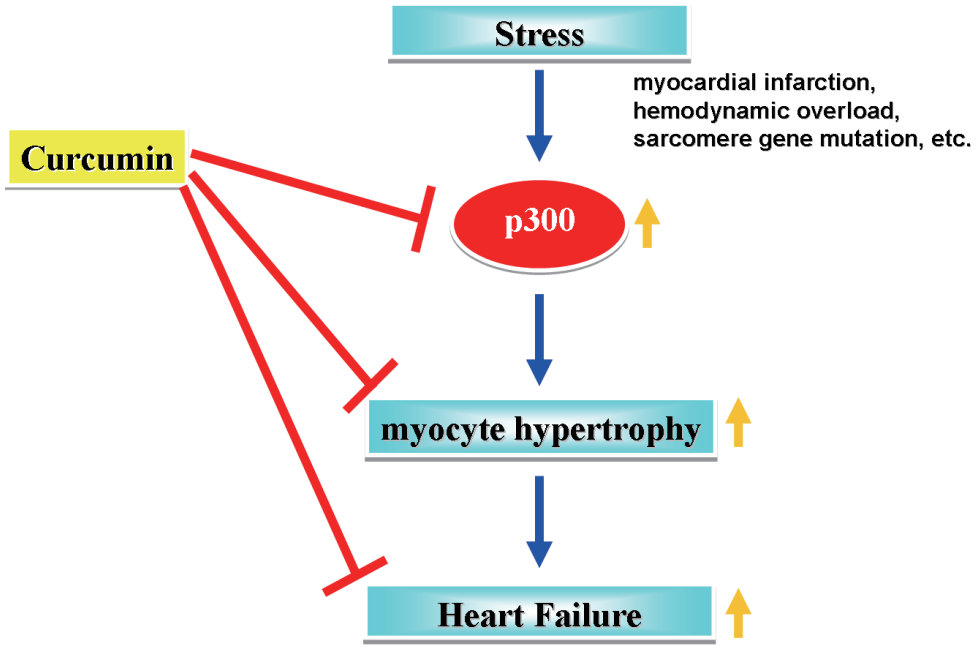

Fig. 3. **Curcumin inhibits p300 HAT activity and thereby the progression of cardiomyocyte hypertrophy and heart failure.**

when combined with such antihypertensives.

Clinical application of curcumin will require comparison of its efficacy with that of existing therapeutic agents, as well as extensive evaluation of its additive effects. To this end, the efficacies of curcumin and enalapril, an ACE inhibitor and standard therapeutic agent for heart failure, were compared in a rat model of myocardial infarction [18]. Curcumin was able to match the therapeutic effects of enalapril on heart failure, while heart function was additively improved on combination of the two. These findings indicate that curcumin has an additive effect with ACE inhibitors, indicating that its mechanism of action does indeed differ from those compounds and providing further support to the notion that optimum efficacy against cardiac hypertrophy and heart failure may be achieved via combination treatment with antihypertensives.

III) Improvement in heart failure on THERACURMIN® administration

Given that curcumin showed poor oral absorption in rats even at 50 mg/kg/day, we used THERACURMIN® as an alternative in our studies, as orally administrated THERACURMIN® improved post-MI LV systolic dysfunction in rats at much lower doses (0.5 mg/kg) than curcumin [19].

IV) Future heart failure therapy

To establish a fundamental pharmacological therapy for heart failure, we examined the common nuclear signaling pathway within cardiomyocytes, ultimately identifying the p300 HAT activity as a molecular target. In addition, we confirmed that curcumin, a p300-specific HAT inhibitor, inhibited hypertrophy in cultured cardiomyocytes and improved heart failure in animal models, with clinical trials in humans currently ongoing. These above-described findings suggest that a new therapy aimed controlling gene expression in the nuclei of cardiomyocytes as well as cardiomyocyte function may be within reach. Developing such a therapeutic regimen will in turn improve the quality of life and prognosis of patients with heart failure.

4. Development of new cancer therapy using THERACURMIN®

Another potential health benefit of curcumin is its antitumor effects. A Pubmed search using the keywords "curcumin" and "cancer" returned over 1500 articles published since 1983, with more than half published in the past 5 years. Curcumin's antitumor effects have been shown in a number of preclinical cancer models, including breast cancer, colorectal cancer, head and neck cancer, leukemia, stomach cancer, liver cancer, ovary cancer, pancreatic cancer, prostate cancer, and multiple myeloma [20-22]. Curcumin has been reported to affect the expression and activity of various proteins involved in cancer progression, particularly nuclear transcription factor-κB (NF-κB). In cancer tissues, upstream signals (growth factors, cytokines, and hypoxemia) can activate NF-κB, which in turn upregulates the expression of downstream proteins involved in anti-apoptosis (Bcl-2 and Bcl-xL), cell proliferation (cyclin D1 and *c*-myc), angiogenesis (vascular endothelial growth factor [VEGF] and interleukin-6), and metastasis (matrix metalloproteinases [MMP]), all of which can induce cancer progression [23]. Curcumin's NF-κB-inhibiting activity, together with its safety profile supported by its widespread use as a spice and traditional medicine for many years, therefore presents this compound as a promising new anticancer agent (***Fig. 4***).

I) Clinical trials using curcumin

On searching ClinicalTrials (http://clinicaltrials.gov/), a registry of clinical trials, using the keywords "curcumin" and "cancer," we found that the number of clinical trials registered increased from 27 in October 2010 to 34 in May 2011.

In our Phase I/II clinical trial using curcumin in patients with pancreatic cancer who were resistant to gemcitabine, a standard therapeutic agent for pancreatic cancer [25], we evaluated the safety and tolerability of curcumin at 8 g/day in combination with gemcitabine-based chemotherapy. The daily dose of 8 g was selected because although no dose-limiting toxicity had been observed up to a daily dose of 12 g in an overseas Phase I clinical trial of curcumin, no additional increase in the blood concentration was achieved at doses exceeding 8 g, and continuing treatment at doses over 8 g is difficult due to the excessive bulk to be ingested. Because no

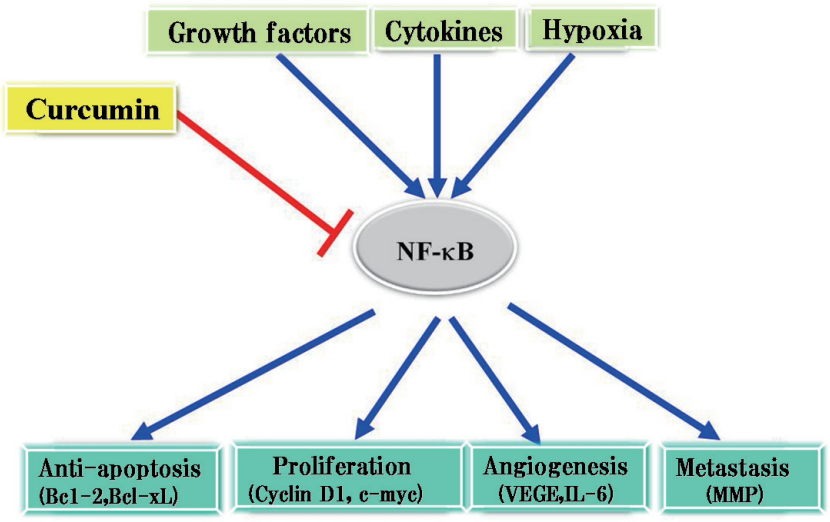

Fig. 4. **Curcumin inhibits the activity of NF-κB, a factor involved in cancer progression.**

predefined dose-limiting toxicity was observed in the first 3 patients, the Phase II clinical trial was continued at a daily dose of 8 g for all 21 patients. No notable adverse events related to concomitant curcumin were reported, and the median compliance was as high as 100% (range: 79%-100%). In all patients, the median survival and one-year survival rate were 161 days (95% confidence interval: 109-223 days) and 19% (95% confidence interval: 4.4%-41.4%), respectively, promising results considering a dismal prognosis of this disease after getting refractory to gemcitabine, despite the relatively small sample size.

However, while the above findings are indeed promising, curcumin's low bioavailability still compromised its clinical application. A number of studies have cited extremely low blood curcumin concentrations (***Table 1***), indicating that curcumin bioavailability needs to be improved to exert significant therapeutic benefits.

Table 1 Previously reported blood curcumin concentrations

Subject	Dose of curcumin	Sample size	Plasma curcumin level (mean±SE)	Reference
healthy volunteers	2 g/day	8	6 ± 5 ng/ml	26
patients with precancerous lesions	8 g/day	2	651 ± 688 ng/ml	27
patients with colorectal cancer	3.6 g/day	3	4 ± 0.2 ng/ml	28
healthy volunteers	12 g/day	3(1)	57 ng/ml*1	29
patients with colorectal cancer	3.6 g/day	3	below 1 ng/ml	30
healthy volunteers	8 g/day	6	2300 ± 260 ng/ml	31
patients with pancreatic cancer	8 g/day	5	134 ± 70 ng/ml	25

*1 Blood curcumin concentration detectable in only 1 patient

II) New clinical trials using THERACURMIN®

In Japan and abroad, efforts are now being made to improve the bioavailability of curcumin by developing new formulations using various drug delivery systems (liposomes, nanoparticles, and phospholipids) as well as derivatives with higher activity. In one pharmacokinetic study, maximum blood concentration (C_{max}) in 6 healthy volunteers after ingestion of THERACURMIN® at a dose of 150 mg was 189 ± 48 ng/mL (mean ± standard error), which was higher than that observed with conventional curcumin at a daily dose of 8 g. The same 6 subjects also received THERACURMIN® at a dose of 210 mg after a 2-week period, resulting in a C_{max} of 275 ± 67 ng/mL. These results further demonstrate the markedly improved bioavailability of THERACURMIN® compared with curcumin and dose-dependently increased blood curcumin concentration up to 210 mg in human [3]. In light of these findings, THERACURMIN® is expected to provide more reliable effects with higher blood curcumin concentrations, and a new clinical trial using THERACURMIN® is now underway to test its efficacy in cancer patients.

5. Efficacy of exercise and potential effects of curcumin on arterial stiffness

William Osler once stated, "a man is as old as his arteries". Accordingly, stiffness of the central arteries such as the aorta (arterial stiffness) increases with aging and is an independent risk factor for cardiovascular disease. In the past, little attention was paid to the potential effects of habitual exercise and eating habits on arterial stiffness, because the increase in arterial stiffness was traditionally considered an irrevocable phenomenon of aging. However, since the discovery of the link between habitual aerobic exercise and decreased arterial stiffness, increasing focus has been situated on the importance of exercise in decreasing arterial stiffness. A similar relationship has been identified between diet and arterial stiffness. In this section, we review the relationship between exercise and diet with arterial stiffness, as well as touch on the latest findings regarding the relationship between arterial stiffness and curcumin in particular.

I) Exercise and arterial stiffness

Arterial stiffness is a risk factor for cardiovascular and cerebrovascular diseases that increases with age. To counter these risks, increased physical activity and habitual exercise in daily life may help prevent or inhibit this stiffness, thereby slowing the development of cardiovascular and cerebrovascular diseases in middle-aged and older people. Indeed, arterial stiffness has been shown to be lower in middle-aged and older people who exercised regularly such as by jogging, walking, or cycling than in those who did not [32]. Similar findings were found in those with high levels of physical activity in their daily lives [33] or in those who took up relatively short-term aerobic exercise regimens (over 2 to 3 months) [32,34,35], all findings which support the notion that habitual aerobic exercise decreases arterial stiffness. Further, these findings are not limited to merely fit, middle-aged individuals, as habitual aerobic exercise-induced decreases in arterial stiffness have also been noted in both the young and elderly as well as in the obese [32,34-37].

Regarding the mechanism for these effects, we previously reported the involvement of endothelin-1, which is produced by vascular endothelial cells and has a vasoconstrictive effect and a stimulatory effect on vascular smooth muscle proliferation [38]. In middle-aged and older people who received exercise therapy for 3 months, acute administration of an endothelin receptor antagonist decreased arterial stiffness before exercise therapy but had no effect on stiffness after exercise therapy, when both the plasma endothelin-1 concentration and arterial stiffness had already decreased [38]. These findings strongly suggest that habitual aerobic exercise may decrease arterial stiffness by decreasing the production of or sensitivity to endothelin-1.

II) Diet and arterial stiffness

Various studies have shown that not only habitual exercise, but also eating habits can decrease arterial stiffness. In one study in obese individuals, diet improvement with calorie restriction over 3 months resulted in a mean weight decrease of approximately 8 kg as well as a decrease in arterial stiffness [39]. In addition, many studies have reported how certain diets may affect arterial stiffness [40]. For example, one demonstrated that salt intake substantially affects arterial stiffness as well as blood pressure [41,42]. A cross-sectional study showed that a decrease in salt intake results in not only a decrease in blood pressure but also in arterial stiffness, independent of blood

pressure [41]. In a longitudinal study in postmenopausal women with hypertension, arterial stiffness was decreased after 3 months on a low-salt diet [42]. Interestingly, the decrease in stiffness was more pronounced following a change in diet than that achieved with habitual exercise [42]. Besides salt reduction, fish consumption has also been reported to help reduce arterial stiffness, as increased consumption has been associated with decreased arterial stiffness [43], suggesting that the polyunsaturated fatty acids in fish oil, abundant in blue-skin fish such as mackerel, saury, and sardine, may be involved in decreasing arterial stiffness. In addition, a number of studies have shown a decrease in arterial stiffness due to the isoflavones in soybeans, pungent chili powder, antioxidant vitamins (vitamin C and vitamin E), garlic powder, and milk-derived lactotripeptides.

III) Curcumin and arterial stiffness

We recently evaluated the effects of continuous use of curcumin on arterial stiffness. In postmenopausal middle-aged and older women, arterial stiffness decreased after use of THERACURMIN® over a period of two months (unpublished data), with efficacy almost equal to that achieved with aerobic exercise over the same period. These findings suggest that curcumin may be an alternative therapy to decrease arterial stiffness in patients who cannot or will not continue exercise. We also evaluated the effects of combining habitual aerobic exercise and THERACURMIN® on arterial stiffness, finding that arterial stiffness decreased more markedly with combination therapy than with either alone (unpublished data).

IV) To improve arterial stiffness

We demonstrated that the arterial stiffness is decreased by curcumin ***(Fig. 5)***. Furthermore, we suggest that maximizing the effects of curcumin against arterial stiffness can best be achieved by combining habitual exercise and eating habits. Such a combination of exercise and diet with curcumin may represent a remarkably effective non-pharmacological therapy.

6. Conclusion

Japan's rapidly aging society is experiencing increased social demand for healthy longevity. Meeting this demand via development of new highly functional food-derived substances and medicinal seeds from foods will require organically combining nutritional, pharmaceutical, and medical sciences using new methodologies and technologies. Studies to date have evaluated the interactions between pharmaceutical products and foods or their safety on an individual rather than comprehensive basis. As reviewed in this article, many studies ranging from basic studies to clinical studies have been conducted on curcumin and its clinical applications in treating various diseases. Given its range of effects, curcumin alone may be useful in treating and preventing a number of diseases, but fully establishing its potential will require further studies and clinical application.

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Conflict of interest statement:

The authors declare no financial or other conflicts of interest in the writing of this paper.

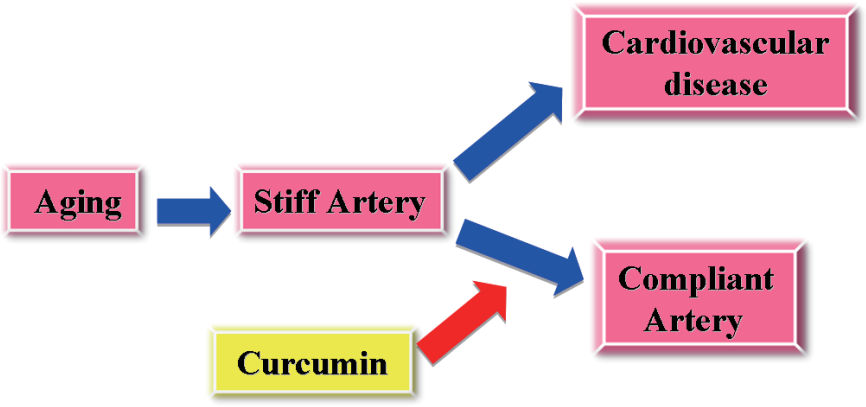

Fig. 5. **Curcumin improves artificial stiffness.**

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