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Clinical applications of curcumin

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ABSTRACT

The morbidity of lifestyle-related diseases such as heart disease, cancer, and diabetes mellitus is increasing in industrialized countries including Japan each year, and dealing with this increased morbidity is a problem that needs prompt attention. Curcumin is a natural polyphenol derived from the root of *Curcuma longa* and has multiple actions, such as anti-inflammatory action, anti-cancer action, anti-oxidant action, anti-viral action, and cytoprotective action. It is expected that curcumin has therapeutic potency to prevent various lifestyle-related diseases. However, curcumin is not readily soluble in water and has an extremely low level of bioavailability. Over the past decade, preparation techniques such as nanoparticles and micelles have led to the development of highly absorbable curcumin preparations, paving the road for human use of curcumin. This article summarizes a number of basic studies and clinical trials involving curcumin and discusses the potential for clinical use of curcumin.

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1. Introduction

As a result of lifestyle changes such as dietary life, exercise habits, rest, smoking, and alcohol consumption, patients with lifestyle-related diseases such as heart diseases, cancer, and metabolic syndromes are increasing each year in industrialized countries including Japan. Over the past several decades, advances in drug research have led to the development of numerous mono-target drugs. However, numerous diseases are caused by abnormalities in multiple signaling pathways, so blocking only one signaling pathway might be insufficiency and inefficiency [1]. In addition, mono-target drugs are extremely difficult and expensive, and they also have the possibility to produce unexpected adverse effects. Recently, it is revealed that ingredients in food act to prevent various developing diseases with abnormalities in biological regulatory system in the body. Foods with these actions are known as functional foods and have garnered attention. Functional foods with multi-faceted actions and a low price have become more important than mono-target drugs in terms of preventing various diseases [2].

Curcumin is a polyphenol and derived from the rhizome of *Curcuma longa*. Curcumin has long been used as a spice in curry, a natural coloring agent, and Chinese and Indian traditional medicines. In the US, the FDA has approved curcumin as a safe ingredient in food. In Japan, curcumin is used in foods such as curry, pickled radishes, and Japanese confectioneries. The latest

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research has revealed that curcumin has various physiologic activities, and worldwide attention has focused on curcumin. Curcumin has been found to have multiple actions such as anti-inflammatory action through inhibition of NF-kB; anti-cancer action through cell-cycle arrest, induction of apoptosis, and inhibition of angiogenesis; anti-oxidant action through removal of free radicals and an increased intracellular concentration of glutathione; anti-viral action; and cytoprotective action. Moreover, numerous studies using biotechnology techniques have reported that curcumin regulates intracellular signaling pathways associated with various chronic diseases (Table 1) [3]. Naturally derived curcumin is a pleiotropic molecule and might be effective at treating various diseases such as cancer, heart disease, and metabolic syndrome. Numerous human clinical trials involving curcumin are undergoing in Japan and elsewhere around the world. At the current point in time, 23 clinical trials involving curcumin are registered in UMIN-CTR (http://www.umin.ac.jp/ctr/), and 108 clinical trials are registered in ClinicalTrial.gov (https://clinicaltrials.gov/), a website where foreign clinical trials are registered (Table 2) [4]. This article has summarize numerous basic studies and human clinical trials of curcumin in Japan and the world and discuss the potency for clinical use of curcumin.

2. Approaches to clinical use of curcumin

Because curcumin is highly lipophilic, poor gastrointestinal absorption, and mostly eliminated without being absorbed at oral administration, curcumin has an extremely low level of bioavailability. According to a study by Lao et al., the maximum concentrations of curcumin in the blood when orally taking 10 or 12 g of curcumin were 50.5 and 57.6 ng/ml, respectively [5]. Thus, the approach to improve absorption efficiency of curcumin is required for exhibiting therapeutic potency of curcumin in humans. Some studies demonstrated that the preparation of curcumin nanoparticles or curcumin in micelles and liposomes improve curcumin absorption on oral intake in humans. One of these approaches is BCM-95, a preparation that mixes microparticles of curcumin with essential oil of turmeric. The relative bioavailability of BCM-95 exhibited a 6.9-fold increase in humans compared to natural curcumin [6]. Meriva is a preparation containing soybean lecithin (a mixture of phospholipids) complexed with curcumin to produce micelles. A human clinical trial revealed that Meriva resulted in a 29-fold improvement in absorption efficiency in comparison to natural curcumin [7]. In our previous study, Theracurmin is produced by preparing nanoparticles of curcumin with gum ghatti coating [8]. In a trial that orally administered Theracurmin 30 mg to humans, the area under the blood concentration-time curve (AUC) of Theracurmin was 27.5 times higher than those of natural curcumin. The maximum concentration of curcumin in the blood was 29.5 ng/ml. This level is comparable to those of natural curcumin intake in gram doses. Curcumin preparations such as BCM-95, Meriva, and Theracurmin can easily achieve a satisfactory concentration of curcumin in the blood at low doses intake compared to natural curcumin powder. Thus, these curcumin preparation may be useful for clinical setting to treat various diseases in the future. Our current study demonstrated a double-blind crossover human trial to compare these 3 preparations and revealed that Theracurmin resulted in an AUC 16.1 and 5.6 times higher than those of BCM-95 and Meriva, respectively [9]. Theracurmin is highly orally absorbable in comparison to the other curcumin preparations and may be the most effective curcumin preparation to exhibit its various actions. Until the present time, various clinical trials involving Theracurmin are undergoing in Japan and the US (Table 2).

Table 1
Molecular targets of curcumin.

Inflammation	IL-1, -2, -6, -8↓
	TNF-a↓
Kinase activity	EGFR kinase↓
	MAPK↓
	PKA↓, PKB↓, PKC↓
	JAK↓
Transcriptional factor	AP-1↓
	β-Catenin↓
	CREB↓
	NF-kB↓
	PPARγ↑
	STAT3↓
	p53↓
	c-myc↓
	HIF1↓
Enzyme activity	COX-2↓
	iNOS↓
	MMP↓
	p300↓
Etc	Cyclin D, Cyclin E↓
	Bax↑, Bcl-2↓
	VEGF↓
	Adiponectin↑
	GST↑, Glutathione↑
	ROS↓

2.1. Cancer

In various physiologic activities of curcumin, its anti-cancer action has been investigated. A search of PubMed (a website for searching life science literature) for journal articles related to curcumin and cancer resulted in over 2700 articles since 1983. These articles has doubled over the last 5 years. The reason for the efficiency of curcumin against cancer is because curcumin targets multiple signaling pathways. Curcumin acts multiple-molecules associated with the progression of cancer by inducing apoptosis (Bcl-2 and STAT3) and inhibiting cell proliferation (c-myc and Cyclin D1), angiogenesis (VEGF and IL-6), and metastasis (MMP) [10]. *In vitro* experimental systems using cultured cells and animal experiments demonstrated that curcumin has effective in the treatment of colon cancer, pancreatic cancer, liver cancer, prostate cancer, breast cancer, and thymus cancer [4]. Clinical trials involving use of curcumin for patients with various cancers are going. Kanai et al. performed a phase I/II clinical trial using curcumin for patients with gemcitabine-resistant pancreatic cancer [11]. Although this trial analyzed only 21 patients, taking curcumin 8 g/day resulted in a median survival of 161 days (95% confidence interval: 109–223 days) and a 1-year survival rate of 19% (4.4–41.4%). Because the prognosis of patients with gemcitabine-resistant pancreatic cancer is generally close to 60 days, these finding are promising. At present, a phase II clinical trial involving use of Theracurmin for patients with pancreatic cancer have been going (Table 1). In the US, the M D Anderson Cancer Center also conducted a phase II clinical trial in patients with advanced pancreatic cancer, and this trial indicated that taking curcumin 8 g/day resulted in reduced phosphorylation of NF-kB, COX2, and STAT3 in peripheral blood mononuclear cells from patients [12]. It is noted that one patient had 73% tumor reduction. This institution currently have performed a phase I clinical trial using Theracurmin for the patients with various cancers in order to determine its safety and maximum tolerated dose. Further research using Theracurmin may lead that curcumin therapy contribute to improve quality of life and a prognosis for patients with cancer.

2.2. Heart failure

Hemodynamic stresses including hypertension or myocardial infarction activate neurohumoral factors such as the sympathetic