Curcumin reduced fat accumulation in *Caenorhabditis elegans*

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Curcumin, the primary bioactive substance in turmeric, is known to be associated with weight loss. In this study, we employed *Caenorhabditis elegans*, a well-established in vivo nematode model to explore the role of curcumin in regulating lipid metabolism. *C. elegans* administrated with curcumin (10, 25 and 50 \(\mu\)M) exhibited significantly reduced fat accumulation, along with smaller body size (width) when compared to the control, without significantly affecting the feeding behavior. Locomotive activity (average moving speed) was significantly increased by curcumin treatment, suggesting a potential increase in energy expenditure. The reduced fat accumulation by curcumin was dependent on lipogenesis-associated genes, sbp-1 (encodes the homolog of sterol response element binding proteins) and fat-6 (encodes a homolog of stearoyl-CoA desaturase), as curcumin significantly down-regulated the expression levels of these two genes and its fat reduction effect was null by the mutation of sbp-1 and fat-6. Additionally, the increased locomotive activity by curcumin was dependent on sbp-1. Current results suggest that curcumin decreases fat accumulation by inhibiting sbp-1/fat-6-mediated signaling in *Caenorhabditis elegans*.

1. Introduction

In recent decades, incidence of obesity is increasing at an alarming rate worldwide and continues to be a major global public health concern. In the United States, the prevalence of obesity increased from 30.5% to 42.4%, and the prevalence of severe obesity increased from 4.7% to 9.2% from 1999 to 2018 (Centers for Disease Control and Prevention, 2020). Therefore, increasing attention has been given to obesity treatment, 2020. Thus, in the current research, we investigated the role of curcumin in lipid metabolism in *C. elegans*.

2. Materials and methods

2.1. Materials

Curcumin (C1386, CAS-No. 458-37-7) was purchased from Sigma-Aldrich Co. (St. Louis, MO). Biological agar and other chemicals for *C. elegans* maintenance were all purchased from Thermo Fisher Scientific Inc. (Middletown, VA), unless otherwise stated. Ampicillin and carbenicillin were purchased from Sigma-Aldrich Co. (St. Louis, MO). Household bleach (The Clorox company, Oakland, CA) was obtained in a local supermarket. Reagents for triglyceride (Triglyceride, Infinity™ Triglyceride Reagent) and protein (Bio-Rad DC protein assay kit) measurement were purchased from Thermo Fisher Scientific Inc.

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C. elegans strains were maintained as previously described (Yue et al., 2019) in nematode growth medium (NGM) with freshly prepared *Escherichia coli* OP50 as the food source. The synchronized population was prepared by the standard bleaching method (Yue et al., 2019). Treatments were administrated in a liquid S-complete medium, along with ampicillin (100 μg/mL), carbenicillin (50 μg/mL), *E. coli* OP50 (8 mg wet weight/mL) and curcumin in dimethyl sulfoxide (DMSO) with a final concentration of 0.1% DMSO. Based on the previous publication of curcumin in *C. elegans* where up to 200 μM curcumin improved survival after oxidative stress (Yu et al., 2014), dosages of 10, 25 and 50 μM were chosen in the current study. For all experiments treatments were started from the 1st day of adulthood for 2 days at 20 °C.

### 2.2. *C. elegans* culture

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### 2.3. Triglyceride and protein measurement

Triglyceride and protein measurements were performed as previously reported (Yue et al., 2019). After treatment, worms were collected and washed thrice with sterilized water. Samples were prepared by sonication in 0.05% Tween 20 for 3 min. Triglyceride and protein were measured using the Infinity™ Triglyceride Reagent and Bio-Rad DC protein assay kit, respectively, according to the manufacturer’s instructions. Protein content was used as the internal control to normalize the triglyceride level.

### 2.4. Pharyngeal pumping rate, worm size and locomotive activity

The pharyngeal pumping rate was recorded as previously reported (Yue et al., 2019). After treatment, 12 worms per treatment were randomly selected and the pumping rate was monitored by counting the pharyngeal contraction under an optical microscope for 30s. Body size (length and width) and average moving speed were determined by the WormLab Tracking system (MBF Bioscience, Williston, VT) as previously described (Yue et al., 2019). Pre-treated worms were transferred to a low peptone NGM plate seeded with a thin layer of freshly prepared *E. coli* OP50. After 10 min of acclimation, a 1 min video was recorded and analyzed with the WormLab software (MBF Bioscience version 3.1. 0, Williston, VT) for body size and average moving speed.

### 2.5. Reverse transcription quantitative real-time PCR

Real-time PCR was performed as previously described (Yue et al., 2019). Total RNA was extracted by Trizol. A high-capacity cDNA reverse transcription kit was used to generate cDNA. Real-time PCR was performed using the StepOnePlus™ Real-Time PCR system (Applied Bio- systems, Foster City, CA). TaqMan™ gene expression assays used were sbp-1 (Ce02453000_m1), fat-6 (Ce02465318_g1) and ama-1 (Ce02462726_m1, an internal control).

### 2.6. Fatty acid composition analysis

Total fat were extracted and methylated as previously described (Colmenares et al., 2016). Fatty acid methyl esters were then injected for GC/MS analysis (Shimadzu GCMS-QP2010 SE, Tokyo, Japan) using Supelcowax-10 fused silica column (100 m × 0.25 mm i.d., 0.25 μm film thickness, Sigma-Aldrich, St. Louis, MO) with helium as the carrier gas. Temperature of injector was 250 °C. Running condition was initial temperature at 50 °C, increased to 200 by 20 °C/min, held for 30 min then increase to 220 °C by 2 °C/min and hold for 162.5 min. MS interface was 220 °C and ion source was 200 °C. An electron ionization (EI) with 70 eV with full scan mode in 35–500 m/z range with 0.3× of scan time were used. Fatty acid methyl esters were identified by comparing with standards and/or their mass spectra in the National Institute of Standards and Technology (NIST) Mass Spectral Library as previously described (Yue et al., 2019). The desaturation index was calculated as % of oleic acid over % of stearic acid (Yue et al., 2019).

### 2.7. Statistical analyses

Data were presented as mean ± S.E. Using SAS Software (version 9.4, SAS Institute, Cary, NC), results were analyzed by one-way analysis of variance (ANOVA), followed by the Tukey’s multiple comparison test for the comparisons among groups. *P* < 0.05 was considered statistically significant.

### 3. Results

#### 3.1. Curcumin reduced fat accumulation of *C. elegans*

As shown in Fig. 1, curcumin at concentrations of 10 μM (*P* = 0.0025), 25 μM (*P* < 0.0001), and 50 μM (*P* < 0.0001) significantly reduced fat accumulation in *C. elegans* by 7–15% when compared to the control group, while no significance was observed in the 5 μM curcumin-treated group. This suggests that curcumin dose-dependently reduced fat accumulation at concentrations equal to and higher than 10 μM in *C. elegans*.

#### 3.2. Effect of curcumin on food intake, body size, and locomotive activity

Next, we examined the effect of curcumin on several physiological parameters: food intake, body size, and locomotive activity. Curcumin at both 10 and 25 μM did not influence the pharyngeal pumping rate, a food intake indicator, suggesting that the feeding behavior was not influenced by curcumin (Fig. 2A). Locomotive activity was measured as the average moving speed, which was significantly increased by curcumin at 10 (29% increase, *P* = 0.0073) and 25 μM (32% increase, *P* = 0.0031) compared to the control (Fig. 2B). This suggests that the increased energy expenditure caused by curcumin might be a potential contributor to the observed fat-lowering effect of curcumin (Shen et al., 2018a). Moreover, nematodes from curcumin groups showed
significantly decreased worm width (Fig. 2C) at 10 μM (12% decrease, \( P = 0.0034 \)) and 25 μM (10% decrease, \( P = 0.0352 \)) compared to the control, while no significance was observed on worm length (Fig. 2D). The reduced body size is likely due to the reduced overall fat accumulation by curcumin. Taken together, these results suggest that curcumin, at 10 or 25 μM, reduced the body size and increased locomotive activity without changing the food intake in *C. elegans*.

3.3. Curcumin reduced fat accumulation via sbp-1 and fat-6

To explore the underlying molecular target(s) of curcumin’s fat reduction, real-time PCR and gene knock-out mutant strains were employed to identify the role of curcumin in lipid metabolism. SBP-1, the single homolog of sterol response element binding proteins (SREBPs), plays a crucial role in regulating lipogenesis (Shen et al., 2018b; Xiao and Song 2013). It acts as the upstream regulator of stearoyl-CoA desaturase (SCDs) that are responsible for catalyzing the rate-limiting step in the formation of monounsaturated fatty acids from saturated fatty acids (Shen et al., 2018b). It has been suggested that SCDs are potential drug targets for obesity treatment (Cohen et al., 2003; Dobrzyn and Ntambi 2005) as deficiency in SCDs has resulted in overall fat reduction in both mammals (Dobrzyn and Ntambi 2005; Cohen et al., 2003) and *C. elegans* (Shen et al., 2018b). In *C. elegans*, SCDs are encoded by fat-5, fat-6, and fat-7. Therefore, we examined the effect of curcumin on the *sbp-1*, *fat-5*, *fat-6*, and *fat-7* mutant strains. As shown in Fig. 3A, the fat lowering effect of curcumin was successfully abolished in the *sbp-1* and *fat-6*, but not *fat-5* and *fat-7* mutants, indicating the genetic requirement of *sbp-1* and *fat-6* for curcumin’s fat reduction effect. To further delineate the role of curcumin on *sbp-1* and *fat-6*, we next performed real-time PCR on these two genes in wild-type nematodes. As shown in Fig. 3B, the mRNA expression levels of *sbp-1* and *fat-6* were significantly down-regulated by curcumin treatment, suggesting that curcumin inhibits *sbp-1* and its target *fat-6* to reduce fat accumulation in *C. elegans*.

*nhr-49*, a gene that encodes a functional homolog of peroxisome proliferator-activated receptors (PPARs) in *C. elegans* (Shen et al., 2018b; Van Gilst et al., 2005), is another upstream regulator of SCDs, and also plays an essential role in regulating fatty acid β-oxidation (Shen et al., 2018b; Van Gilst et al., 2005). However, a mutation of *nhr-49* failed to abolish the effect of curcumin on fat reduction (Fig. 3A), suggesting that *nhr-49* is not necessarily a contributor to curcumin’s effect on SCDs and fat accumulation.
**aak-2** encodes one of the subunits that was suggested to be responsible for the kinase activity of AMP-activated protein kinase (AMPK), an energy sensor that regulates metabolic energy balance at the whole-body level (Hardie et al., 2012). As observed in wild type N2 worms, curcumin significantly reduced fat accumulation in *aak-2* mutant nematodes (Fig. 3A), suggesting that *aak-2* may not be an essential genetic requirement for curcumin’s fat reduction effect. Collectively, these results suggest that curcumin reduced fat accumulation via *sbp-1/fat-6*-mediated signaling.

3.4. Curcumin significantly reduced fatty acid desaturation index

To further determine the roles of *sbp-1/fat-6* in curcumin’s fat reduction effect, fatty acid composition of *C. elegans* was analyzed. As shown in Fig. 4, the desaturation index, the conversion rate of stearic acid to oleic acid, was significant reduced by curcumin treatment at 25 μM by 34% when compared to the control group (*P* = 0.0124), while no significant effect was observed at 10 μM curcumin treatment.

3.5. Curcumin altered locomotive activity via *sbp-1*

Since treatment of curcumin significantly increased the locomotive activity in wild-type nematodes, we determined next if this effect of curcumin is also mediated by *sbp-1* and *fat-6* using mutant strains. Additionally, since it is known that AMPK activation is positively related to locomotive activity in *C. elegans* (Shen et al., 2018a), the effect of curcumin in the *aak-2* mutant was also examined to determine if curcumin increased locomotive activity via *aak-2*.

No significant change was observed in the average moving speed between the control and curcumin-treated *sbp-1* mutants (Fig. 5A), which indicates that curcumin’s effect on locomotive activity was fully abolished by the *sbp-1* mutation. However, curcumin treatment significantly increased the average moving speed in the *fat-6* and *aak-2* mutants, dose-dependently (Fig. 5B and C). *fat-6* mutants exhibited 29% (*P* < 0.0001) and 69% (*P* = 0.0028) increases, and *aak-2* worms showed 21% (*P* = 0.0419) and 27% (*P* = 0.0041) increases at 10 and 25 μM, respectively, compared to the control groups. These observations suggest that these two genes, *fat-6* and *aak-2*, are not the genetic requirement for curcumin’s effect on locomotive activity. Taken together, the results above suggest that the increased locomotive activity by curcumin was dependent on *sbp-1*.

**Fig. 4.** Effect of curcumin on the desaturation index. Synchronized 1st day adult worms were treated with control (0.1% DMSO) or curcumin (10 and 25 μM in DMSO) for 2 days at 20 °C. After treatment, fatty acid composition of worms were analyzed by GC/MS and the desaturation index were calculated as % of oleic acid/% of stearic acid. Results are expressed as mean ± S.E. (*n* = 3 plates, each plate >6000 worms). Means with different letters are significantly different at *P* < 0.05.

**Fig. 5.** Effect of curcumin on locomotive activity. Synchronized 1st day adult *sbp-1*, *fat-6*, and *aak-2* mutant worms were treated with control (0.1% DMSO) or curcumin (10 and 25 μM in DMSO) for 2 days at 20 °C. After treatment, worms were transferred to a fresh *E. coli* OP50-seeded low-peptone plate, locomotive activity of *sbp-1* (A), *fat-6* (B) and *aak-2* (C) mutant worms were monitored and analyzed by the WormLab Tracking System. Results are expressed as mean ± S.E. (*n* = 29–30 for *sbp-1*; *n* = 26–29 for *fat-6*; and *n* = 25–30 for *aak-2*). Means with different letters are significantly different at *P* < 0.05.

4. Discussion

In the present study, curcumin at concentrations ≥10 μM significantly reduced fat accumulation in *C. elegans* without affecting the feeding behavior. Worm width was significantly reduced under curcumin treatment, likely due to the reduced fat content, as seen in previous publications (Farias-Pereira et al., 2018; Shen et al., 2017a). These effects of curcumin were dependent upon *sbp-1* and its target *fat-6*, as seen
in reduced gene expression and fully abolished effects on fat accumulation in \( \text{sbp-1} \) and \( \text{fat-6} \) mutant strains. In addition to elucidate the \( \text{sbp-1} \) dependent fat-reduction mechanisms of curcumin, current study was also the first study that identified the role of \( \text{sbp-1} \) by curcumin in regulating locomotive activity.

\( \text{SBP-1} \), a homolog of \( \text{SREBP} \) transcription factor, is a crucial regulator that facilitates fat storage in \( \text{C. elegans} \). Knockdown of \( \text{sbp-1} \) caused a reduction in overall body fat storage, body size, and brood size, and it altered the expression of lipogenesis-related genes such as \( \text{SCDs} \) (Yue et al., 2019; Shen et al., 2018b). Our results showed that curcumin decreases fat accumulation via \( \text{SBP-1}/\text{SCDs} \)-mediated signaling, which is consistent with a previous report in rodent models (Ding et al., 2016). Similar to curcumin, other functional food ingredients, such as piceatannol (Shen et al., 2017a), cranberry extract (Sun et al., 2016), green coffee extract, 5-O-caffeoylquinic acid (Farias-Pereira et al., 2018), and hesperidin (Peng et al., 2016) were also reported to regulate lipid metabolism via \( \text{sbp-1} \)-mediated mechanisms, indicating that \( \text{sbp-1} \) may be a useful therapeutic target of bioactive components for obesity prevention and treatment.

The current results show that 25 \( \mu \text{M} \) curcumin significantly reduced the desaturation index over the control, which is consistent to reduced \( \text{fat-6} \) expression by curcumin treatment (Fig. 3B). However, curcumin treatment at 10 \( \mu \text{M} \) did not significantly reduce the desaturation index over the control. As the downstream targets of \( \text{sbp-1} \), both \( \text{fat-6} \) and \( \text{fat-7} \) encode delta 9 desaturase with more than 80% genetic homology (Van Gilst et al., 2005) and the compensatory mechanism of each other has been reported (Brock et al., 2006). Thus, it is possible that effects of curcumin at 10 \( \mu \text{M} \) were overcome by the compensatory mechanism of \( \text{fat-7} \), while this may not be enough at 25 \( \mu \text{M} \) curcumin treatment. However, butein, a flavonoid found in annatto seeds and lacquer trees, reduces fat accumulation dependent on \( \text{fat-7} \), but not \( \text{fat-6} \), without significant changes on the desaturation index (Farias-Pereira et al., 2020). The different results of the desaturation index between the current and Farias-Pereira et al. (2020) may be explained that \( \text{fat-6} \) occurs to be a more essential contributor for this desaturation process, as \( \text{fat-6} \) mutant displays significant changes of increased stearic acid and decreased oleic acid, while no significant differences in desaturation were observed in \( \text{fat-7} \) mutant (Brock et al., 2006).

Locomotive activity is known to be regulated by the nervous system (Gjorgjieva et al., 2014; Kleinh and Dougherty), and curcumin has been reported to improve locomotive activity in various disease models of neuropathies via its neuroprotective effects, as well as its ability to stimulate axonal regrowth in rodents (Caillaud et al., 2020). Consistently, in the current study we observed that curcumin significantly increased the locomotive activity of \( \text{C. elegans} \), dependent on \( \text{sbp-1} \). The mechanisms for how \( \text{sbp-1} \) modulates locomotive activity are unclear; however, considering that \( \text{sbp-1} \) is expressed in both intestinal and amphid neurons (Wormbase), it is possible that neuronal \( \text{sbp-1} \) may play a role in this modulation, and hence may alter the locomotion of \( \text{C. elegans} \). The exact mechanisms for how \( \text{sbp-1} \) contributes to the alteration of locomotive activity by curcumin and the role of how \( \text{sbp-1} \) regulate fat accumulation and locomotion needs further study.

Curcumin was previously reported to be an AMPK agonist (Liu et al., 2017), and AMPK activation was found to be associated with increased locomotive activity in \( \text{C. elegans} \) (Shen et al., 2018a). However, the current results show that \( \text{aak-2} \) appears to be an insignificant contributor to curcumin’s effects on fat accumulation and locomotive activity in \( \text{C. elegans} \), as \( \text{aak-2} \) knockdown failed to abolish curcumin’s effects for both parameters. In addition to \( \text{aak-2} \), \( \text{C. elegans} \) has another gene, \( \text{aak-1} \), that also encodes one of the catalytic alpha subunits of mammalian AMPK (Shen et al., 2018b). Thus, we cannot exclude the possibility that \( \text{aak-1} \) plays a role in the observed effects of curcumin in the current study.

The relation between curcumin and PPARs is a matter of much current debate. Some publications suggest curcumin acts as a PPAR\( \gamma \) ligand (Jacob et al., 2008; Mazidi et al., 2016; Fan et al., 2017), while others indicate curcumin is not a PPAR\( \gamma \) agonist (Narala et al., 2009). Our current results showed that \( \text{nhr-49} \), a functional homolog for PPARs, failed to abolish curcumin’s effect on fat accumulation, which suggests that curcumin does not act via PPARs for its fat-lowering effect in this model.

Though curcumin is well known to have a broad spectrum of health benefits, its poor pharmacokinetic profile compromises its therapeutic potential (Dei Cas and Ghidoni 2019). After oral uptake, curcumin undergoes efficient first-pass metabolism and some degree of the intestinal metabolism, particularly glucuronidation and sulfation, yet has low systemic absorption and availability (Dei Cas and Ghidoni 2019; Sharma et al., 2007). Strategies for improving curcumin’s bioavailability have been extensively studied. These include inhibition of curcumin metabolism with adjuvants as well as the development of innovative solid and liquid oral delivery systems to enhance solubility and improve the pharmacokinetic profile of curcumin (Dei Cas and Ghidoni 2019). However, others suggest taking a cautious approach in consideration of potential adverse effects associated with the increased bioavailability of curcumin (Burgos-Morón et al., 2010). Still, an increasing number of studies have begun to report evidence for therapeutic benefits attributed to curcumin metabolites (Gutierres et al., 2015; Edwards et al., 2017). As \( \text{C. elegans} \) also conserves xenobiotic metabolism pathways (Lindblom and Dodd 2006; Harlow et al., 2018), it is possible that curcumin metabolites may play a role in the observed effects of the current study.

According to the Joint United Nations and World Health Organization Expert Committee on Food Additives, the allowable daily intake (ADI) of curcumin is 0–3 mg/kg body weight, based on a NOEL of 250–320 mg/kg body weight/day in a multigeneration study in rats with a safety factor of 100 (WHO). Human clinical studies of curcumin employed a wide range of dosages from 0.1 to 12 g/day, and some of them have shown promising results for the application of curcumin to the alleviation of markers of various pathologies, such as inflammation, oxidative stress, and liver function, without showing significant side-effects (Mousavi et al., 2020; Saraf-Bank et al., 2019; Ganjalil et al., 2014; Panahi et al., 2016; Dei Cas and Ghidoni 2019; Mohamad et al., 2018). Based on the current results, curcumin at concentrations equal and higher than 10 \( \mu \text{M} \) effectively reduced fat accumulation in \( \text{C. elegans} \). However, given the limitations of the \( \text{C. elegans} \) model (lack of certain organs and a circulatory system), a direct translation of dosages from \( \text{C. elegans} \) to humans is not currently possible (Shen et al. 2017b, 2018b). Effective dosages need to be carefully examined while interpreting current results in other models or human clinical trials.

In conclusion, the current study suggests that curcumin reduces fat accumulation via \( \text{sbp-1}/\text{fat-6} \)-mediated signaling and increases activity via \( \text{sbp-1} \). These results can provide an important foundation for the potential application of curcumin as a bioactive constituent in obesity-prevention and/or treatment.

CRediT authorship contribution statement

Yiren Yue: Methodology, Visualization, Formal analysis, Writing – original draft. Gengxin Hao: Investigation, Methodology, Visualization, Formal analysis. Junhyo Cho: Investigation, Visualization, Formal analysis. Yeonhwa Park: Conceptualization, Project administration, Supervision, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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