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The Protective Effects of Curcumin, Black Pepper and Cumin On Liver and Renal Functions in Association to Gut Microbiota Among Overweight Animal Models

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Abstract

THE CURRENT study aimed to measure the protective effect of spicy foods; Curcumin (Cur), Black Pepper (BP), Cumin (Cu) for liver and kidney functions in association to colonic-gut-microbiota (GM) compositions among overweight animal models. Ten Albino rats groups casually used (n=70): nine obese and control negative group; C-ve). Overweight group fed Orlistat as control positive group (H3; C+ve) while eight obese-groups fed Cur/BP/Cu mixtures or alone in different levels targeting GM compositions (Lactobacillus, Bifidobacteria, Clostridium, and total bacteria) within collected feacal samples (0, 14 and 28 day) by flournace in suit hypridization (FISH). Liver and kidney functions indicated in collected serum by alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with urea, uric acid and creatinin additionally to kidney and liver histopathology analysis. Data presented that ALT and AST levels improved significantly ($P<0.05$) with models fed mixture of Cur/BP/Cu (H10). Also, urea decreased significantly with H9 & H10 fed Cu/Cur and Cur/BP/Cu respectively while creatinine had no significant differences between all groups.Liver samples histopathological revealed focal hepatocellular necrosis and apoptosis in H2, slight cytoplasmic vacuolization of hepatocytes at H3 and H4 while H9 showed focal hepatocellular necrosis associated with mononuclear inflammatory cells infiltration vs. H10 at slight vacuolation of some hepatocytes and slight dilatation of hepatic sinusoids. The kidneys microscopically revealed congestion of renal blood vessel and kidneys sections (H2) and vacuolation of epithelial lining renal tubules sections (H3) while H9 showed necrobiosis of epithelial lining renal tubules and H10 showed no histopathological alterations. Finally, total GM correlated with rat groups fed Cur/BP mixture (H7) nearly same positive control group (H3; C+ve) additionally to different groups arranged H4>H5>H8>H6>H10>H9. Lactobacillus were H4>H3>H7>H8>H5>H6 log10 cells/g fecal samples while Bifidobacterial increased with food consumptions as H4>H3>H9>H7>H10>H8>H6. On the other hand, Clostridium numbers decreased at the end of the experimental as H5>H8>H10>H6>H7>H9>H4>H3. Thus Cur/Bp and Cur/Bp/Cu mixtures have positive effects on counted increased probiotic species (Bifidobacteria and Lactobacillus) while Clostridium numbers negatively decreased. In conclusion, the study indication to promote health benefits to be more valuable causing significant liver and kidney function improvements between obese models, however further human studies are required to elucidate novel mechanisms or pathways.

Key words: Probiotics and prebiotics, *Lactobacillus*, Bifidobacteria, *Clostridium*.

Introduction

Obesity and metabolic syndrome are significant public health concerns because of their high global prevalence and association with an increased risk for developing chronic diseases [1,2] The prevalence of obesity has increased over the past few decades . Obesity has been deemed the leading cause of preventable death [3] and has become a global economic and health burden [4,5].

Obesity is the result of a disruption of energy balance that leads to weight gain and metabolic disturbances that cause tissue stress and dysfunction .Clinical manifestation of these underlying disturbances often present as the parameters

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of metabolic syndrome (MetS), a condition characterized by a clustering of 3 or more of the following components: central adiposity, elevated blood glucose, plasma TGs, blood pressure, and low plasma HDL-cholesterol. In line with national obesity trends in the United States, it has been estimated that ~34% of adults have MetS [6]. The high prevalence of MetS is significant, as classification with MetS increases an individual's risk of cardiovascular disease and type 2 diabetes mellitus by 2- and 5-fold, respectively.

The human healthiness generally affected by daily diet adoptions and consumption that can cause different malnutrition diseases such as obesity. Having high energy intake from dietary food supplementations and/or low energy expenditure results in excessive fat accumulation that is correlated well with the major cause for diabetics, cardio vascular problem and cancer worldwide. Moreover, fatness is one of the most core health problems producing death global because of its significances; metabolic problems with over 650

million obese adults and about 2 billion overweight [7]. Additionally, human gut microbita (GM) recently showed important association with different dietary factors in human health and many different diseases [8-11]. The human intestinal microbita community consists of four major phyla of the bacteria; Bacteroidetes (23%), Firmicutes (49%), Actinobacteria (5%) and Proteobacteria (21%). Most of the Firmicutes sequences (95%) will be members of the Clostridia class (Clostridium coccoides group; C. leptum subgroup and Bacteroides-Prevotella group) containing many genera and species [9, 12]. Additionally, the total GM and relative species levels depend on many factors such as illness, antibiotics, the host immune system, digestive and other secretions, stress and diet [8, 10, 11]. Such impaired GM composition and activity known as dysbiosis has been implicated in the development of intestinal permeability, associated with both inflammation in intestinal and peripheral tissues (e.g. adipose tissue, muscles, liver and brain) [13] and altered glucose and energy homeostasis (i.e. metabolic diseases [11]. Indeed different dietary consumptions such as oligosaccharides present in human milk affected the abundance of some gut microbita groups mainly Bifidobacterium longum and several species of Bacteroides with outcompeting other bacterial species such as E. coli and Clostridium perfringens. A study between cohort of lean and obese mice models presented that there is an association between Bacteroides thetaiotaomicron and low serum branched chain amino acid levels in addition to alleviated diet-induced body weight gain [14-16]. Another study between obese Chinese adolescents' shown significantly decrease of abundance Bacteroides thetaiotaomicron with negative correlation in serum glutamate concentration [15, 17]. On the other hand, the non-flavonoids include phenolic acids such as benzoic and hydroxycinnamic acids in addition to stilbenes that both naturally may be found in gallotannins, ellagitannins, stilbene oligomers, and lignans [18]. Previous data suggested a correlated relationship between the curcumin metabolic effects and colonic gut microbiota compositions [19]. Moreover, numerous phytochemicals in curcumin has anti-inflammatory actions; because of its core primary anti-inflammatory and healthy components (turmeric). However, much more studies are needed using either animals or human models. Dissimilar polyphenols such as on black pepper and curcumin have been described to increase lipolysis through intonation of hormone delicate lipase. Therefore, curcumin shows to promote weight damage in order to decrease fatness occurrence and its significances with any associated syndromes in addition to limit the fatness opposing health effects [10]. The primary medical study cured fatness using a profitable design of curcumin supplementation among overweight helpers at 1 g/day as suggested at extreme daily habit [20] that simply reduced the serum triglyceride ranks significantly and insulin actions developments with no variations of BMI or body fat [21]. Again, another study by [22] demonstrated that curcumin functioned as anti-obesity and anti-inflammatory by deteriorated adiposity adding to fat storing [23]. Additionally, black pepper has been identified by numerous favorable properties such as sexual imitation and fatness because of its focal constituents, Piperine and oleoresin [24]. The effect of different nutritive polyphenol sources that all generally expended as a spice; Curcumin (Cur), Black Pepper (Bp) and Cumin (Cu; Cuminum cyminum L.) whichever alone or in diverse mixtures will be assessed on the occurrence of presence overweight or down weight among overweight animal models in association to colonic microbiota profile. Formerly the study carried out to Evalute the properties of such spiced habits on the health position especially the protective effects on liver and renal functions (kidney and liver functions) additionally to colonic microbiota (GM) compositions between obese models; abundant prospective prebiotics properties for weightiness approach that could be accomplished by moderating lipid digestion due to their functional foods with their bioactive ingredients and biological possessions [18]. Thus, the study presented herein is the first to establish such association of used spice mixtures and the colonic GM targeting liver and renal functions.

Material and Methods

Materials

Spices: all used spices (Curcumin, Black pepper and Cumin) were purchased from Pharmaceutical Science Laboratory, National Research Centre, Egypt. Their chemical compositions have been evaluated using high performance liquid chromatography (HPLC; Phenolic, flavonoids fraction and antioxidant activities and data has been published [25].

Substances: Chemicals used for investigational animal models were acquired from Morgan Company, Cairo, Egypt. Conversely, Colic acid obtained from Sigma company and kits used for serum blood analysis was bought from Gama Trade Company, Cairo, Egypt.

Investigational animal replicas

Eighty male Albino rats have been used to investigate the special effects of diverse used spiced foods on body mass loss and all rats were gained from Vaccine and Immunity Organization, Ministry of Health, Helwan Farm, Cairo, Egypt. Rats fed basal diets were prepared rendering to our permeable distributed data for one week and adapted on water permitted admission before the beginning of the experimental [7]. Rats raised in the animal house at the faculty of Home Economics, Menoufia University, Egypt by regular weight of 200g + 5 g. All rats separated arbitrarily into healthy non-obese negative control group (C-ve; n=8) and nine dissimilar sub-obese groups (n= 70) that were prompted by high fat diet (HFD) feedings for about 4 weeks prior to the investigational start point. All rats were saved with standard healthy disorders fed the appropriate treatment for 30 days after presence similarly separated into ten groups of eight rats each arbitrarily. Overweight nine groups separated to positive obese group (C+ve) and eight obese groups as designated within the investigational plan unit then all rats fed the suitable treatment for 30 days. Collected faecal samples (at 0, 14 and 28 day) were used for the measurement of colonic microbiota composition (total bacteria, Bifidobacteria, Clostridium histolyticum, and Lactobacillus) [11]. Finally all the rats were sacrificed and blood with kidney, heart and liver were collected for histopathology analysis in addition to both lipid and kidney functions.

The experimental design

All animals saved in standard healthy laboratory conditions (25 ± 2 ºC for 12 hour) and adjusted on free access of water and fed for one week basal diet before the start standard of the experimental (healthy and ethical disorders were applied after being approved ≠19- 134 SREC-07-2021).). Dissimilar dietary treatments were observed as following: H1; the control (C–ve) non-obese on normal control's basil diet, H2; obese on normal control's basil diet added with Orlistat as medicinal treatment for body weight loss, H3; obese on only normal control's basil diet (C+ve), H4; obeserats administrated to Curcumin; (Cur; 2 g/Kg BW rat), H5; obese rats received black pepper (Bp; 20 mg/kg or 0.02 g/kg), H6; obese rats received Cumin (Cu; 3 mg/kg or 0.003 g/kg), H7; obese rats received a mixture of Curcumin: Black Pepper as 1:0.01%, H8; obese rats received a mixture of Cumin/Black Pepper as 1:0.01%, H9; obese rats received a mixture of Cumin+ Curcumin as 1:0.01%, H10; obese rats received a mixture of all the Curcumin: Black Pepper: Cumin (1:0.01:1%).Diagram 1.

Serum liver and kidney function analysis

Liver functions were measured as indicated by alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities as described by [26]. Again urea [27] uric acid and creatinin [28] were determined for kidney functions after separating the serum from collected blood samples using chemical kits at the end of the experiment.

Microbiological evaluation

The diversity of molecular techniques such as real-time polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) and ribosomal RNA-(rRNA)-targeted oligo-nucleotides enable important insight into the composition of the human intestinal microbiota [29] by monitoring the composition of the gut microbial community. In this study, the measured microbiotic profile included total numbers, Clostridium, Bifidobacteria and Lactobacilli have been measured in the collected feacal samples by FISH as described previously by our published work [8, 11].

Histopathology examination

At the end of the experiment all group rats were sacrificed and samples from livers and kidney were collected and fixed in 10% neutral buffered formalin, then the samples were dehydrated in alcohol, clear in xylol and embed in paraffin 4µ thick Hematoxylene and eosin stained sections were prepared for histopathological examinations (Zhao et al., 2021).

Statistical analysis

Outcomes were obtainable as means ±SE, arithmetical study using SPSS platform ver.21 (F_test by ANOVA, $P< 0.05$, LSD and Tukey) for any significant changes using the standard analysis of variance as outlined by [30].

Results and Discussion

Kidney and liver functions

Table (1) illustrates the kidney (Creatinine &urea) and liver (ALT & AST) functions as mg/dl blood serum samples. It can be noticed that Creatinine had no significant differences ($P<0.05$) between all used spicy supplementations. However, the lowest significant levels ($P<0.05$; 0.50 mg/dl) with groups H4, H7, and H 10 from the control obese group (H3; C+ve) that were very close to the normal levels with both control H1 and H2 groups (C-ve and Orlistat feeding group). Such three groups (H4, H7 and H10) were feeding different spicy supplemented diets especially with one stable spicy; curcumin that used either alone or mixed with different other spicy (Cur, Cur/Bp, Cur/Bp/Cu; respectively). Additionaly, group H6 that were consuming cumin (Cu) supplementation gave the highest Creatinine levels (0.84 ± 0.42 mg/dl). Also rat groups fed different other treatments; groups H8 and H9 obtained low levels of Creatinine, 0.79 ±0.35 and 0.78±0.33 mg/dl respectively. Additionally, H5 group feeding black pepper supplementations were a little bit at Creatinine levels lower than both previous groups (0.72 ± 0.03 mg/dl; Table 1).

Regarding the measured urea levels that were used as an indicator for kidney function are presented in Table 1. It could be seen that urea ranks were reduced significantly ($P<0.05$) mostly with groups H9 and H10; were on diets added to cumin/curcumin and curcumin/black pepper/cumin respectively in comparison to H3 (C+ve; 53.05±0.52 mg/dl). Their reduced levels reached about 25 mg/dl and that approximately the same levels obtained from groups H1 and H2 (C-ve & Orlistat; Table 1). Also, all groups H4, H7 and H8 were in the next stage of the lowest significant differences ($P<0.05$) obtained levels and that was about 33 mg/dl (Table 1). Again, rats within groups H5 and H6 show the highest levels of about 37 mg/dl and they were consuming black pepper and cumin respectively. So, it can be noticed that kidney functions with group H10 were at the best effective levels that were on diets added with mixture of curcumin/black pepper/cumin.

Table 1 finally, presents also the liver function in responded to ALT and AST levels where ALT levels were in a great reduction with rats group H10 that were feeding on curcumin/black pepper/cumin; reached 66.6±1.30 mg/dl (Table 1) in significant differences ($P<0.05$) from H3 group (C+ve; 104.8±3.37 mg/dl). On the other hand rats in group H4 fed curcumin alone was significant differences ($P<0.05$) at the maximum amount of ALT secretions (84.7±0.70 mg/dl) comparing to all treated groups while the rest of the other groups had medium effects on ALT levels. Regarding AST levels, it can be observed from Table 1 that, AST amounts were greatly decreased on groups H7 and H10 and that were feeding diets supplemented Cur/Bp and Cur/Bp/Cu respectively (about 43 mg/dl). Such levels in Table 1 were very close toward control groups H1 and H2 (C-ve & Orlistat respectively) with no significant differences. On the other hand groups H5 and H6 were on the maximum significant differences ($P<0.05$) produced AST ranks among all the treatments (approximate 71 mg/dl). Thus both ALT and AST used as an indicator for liver functions between all the treated groups shown the best results, effective treatment with obese rats fed mix of curcumin/black pepper/cumin (H10) and such obtained data were confirmed with the other measured parameters between the same treated rats group (H10).

Colonic microbiota evaluation

Many gastrointestinal disorders have shown an association recently with gut microbiome interactions many studies trying to kind the links between gut microbiome compositions and activities with digestive tract disorders such as diabetes, inflammatory bowel disease any obesity. Indeed, obese models show an alteration with gut microbiota in many studies. However, non-of them investigated such correlation with consumed spicy foods. Therefore, colonic microbiota profile has been measured in this study between obese animal models consumed different spicy food in different concentrations. This study aimed to measure the colonic microbita in correlation to being obese or not. It has been also designed to discover the links between the used treated spicy and finally the relative colonic composition. Cumin, black paper and turmeric were added either alone or mixes with each other to the uses obese model. The measured microbiotic profile were included the total colonic bacterial numbers (TB; table 2) in addition to Lactobacillus (Lab; Table 3), Bifidobacteria (Bif; Table 4) and Clostridium (His; Table 5) species. All bacterial species have been evaluated between all the experimental used animal models and data illustrated in the following tables (Table 2-5).

It can be seen that total bacterial numbers of all obese rats at zero time point were at similar levels (Table 2) for almost all rat groups (H2-H10; about 16.00 lag10 cells/g) except the negative control group (healthy bacterial non-obese group; 16.08 log10 cell/g). After 14 days of dietary consumption, total bacterial numbers were increases with most animal model group especially with H2 (control on Orlistat treatment) and that reached 16.09 log10 cell/g feacal samples however H1 and H3 that are (C-ve) and (C+ve) groups shown the changes of total bacterial numbers after the 14 days; has been

increased to 16.15 in contrast to be decreased to15.07 log10 cell/g fecal samples respectively. Regarding the differences of used treatments on the total bacterial numbers it can be notice that H5 group which was consuming black pepper was the biggest total numbers after the 14 days (15.92 log10 cell/g fecal samples). The following most effective treated groups have been seen with groups H7, H4 and H8 as they shown 15.75, 15.69 and 15.07 log10 cell/g fecal samples and they were representing consumptions of Curcumen/black pepper, Curcumen and again the group fed cumin/ black pepper respectively. Finally, the lowest effective groups on total bacterial numbers were observed with obese rats fed mixture of curcumen/black pepper/cumin together (about 14.92 log10 cells/g; Table 2). Additionally and the end of the experimental (after 28 days); total bacterial numbers with the non-obese (C-ve) group seems at stable levels (about 16.13 lag10 cells/ml fecal samples) at all the experimental time points with means of 16.12b that was significantly difference from group rats on H6 and H8-H10. However, H2 and H3 the obese groups on Orlistat and healthy basil diet has different increase levels; their total bacterial numbers raised at all the experimental time points and that reaches the highest levels nearly the same at 28 days (16.09 and 15.93 loge10 cells/g fecal samples).

Concerning the effect of the different spicy foods on total bacterial numbers at 28 days between the obese rats, Table 5 presents that group H7, H4, H5, H8 and H6 were respectively showing levels of total bacteria at 16.12, 15.90, 15.67, 15.45 and 15.22 log10 cell/g fecal samples. They representing group rats fed Cur/BP, Cur, BP, Cu/BP and Cu correspondingly. So all the rats fed BP either alone or mixed with Cu shown growth rate with total bacterial numbers. Again, rat groups fed either Cur or Cu alone shown good responses on total gut microbiota numbers. To conclude up, total bacterial numbers have been presented in Table 7 show different correlations corresponding to the used spicy foods with special refer to the rat groups fed curcumen mixed with black pepper (H7). Such group was nearly the same bacterial level of the control positive group (H3; C+ve) especially at the end of the experimental. The observed effect was followed by different groups as following; H4>H5>H8>H6>H10>H9.

Table (3) demonstrates the colonic microbiota (lactobacillus; Lab) that has been affected by uses different spicy foods between the experimental animal models. It can be seen that the biggest lactobacillus numbers were seen with group H1 such group is presenting the healthy rats group fed normal basil diets. It has nearly the same lactobacillus number all over the experimental time points (0, 14 and 28 days) with mean at about 6.74 lag10 cells/g fecal samples. All the lactobacillus levels compositions has differently changes through the experimental and after consuming the different spicy foods depending on the treatment uses. For instance, obese rats group in H2 group fed Orlistat decreased to 5.52 lag10 cells/ml fecal samples after 14 days and again after 28 days to 5.36 lag10 cells/g fecal samples. Additionally groups H6, H8, H9 and H10 show declined lactobacillus levels only after 14 days treatments they show numbers of 5.20, 5.71, 5.72 and 5.83lag10 cells/g fecal samples respectively. On the other hand, group H5 and H7 have raised lactobacillus levels after consuming their added spicy foods after 14 days. They reach 5.85 and 5.78 log10 cell/g fecal samples and they representing rat group fed BP alone and/or Cur/BP respectively. Moreover, it has been notices from Table (3) and after 28 days that consuming all the uses spicy foods, the lactobacillus numbers have been increased again with rats except groups H9 and H10 that are nearly were similar levels from the start time point (0h) 5.89 and 5.90 log 10 cells/ml fecal samples respectively. To sum up; the most effective rat groups the end of the experimental within the Lactobacillus activities could be arranges as H4>H3>H7>H8>H5>H6 log10 cells/g fecal samples. So used animal models fed normal diet shown the highest lactobacillus numbers even more than orliostat group (H2). Again, group H4 shown the second effective treatment and that was follows again by rats group H7 for mixture of both BP/Cur. So the used BP and /or Cur shown positive effects on gut microbiota species specially lactic acid producer bacteria (Lactobacillus) but such effect was renews by addition alone (as seen with group H10) or mixes (as seen with group H9).

Regarding the other microbiotic bacterial measured species (Bifidobacteria; Bif), Table 4 illustrates it after being affected by different uses spicy foods. It can be notice that the control group (H1; C-ve) got the biggest bacterial number (6.51 lag10 cells/ml fecal samples) at the starting time point (0h) while the other obese groups H2 – H10 show low levels (ranged from 5.50-5.60 log10 cell/ml fecal samples). Again the same group (H1, C-ve) show about the same levels after 14 days. However, it was slightly increased at 28 day to 6.61log10 cells/ml fecal samples.

Additionally, at day 14 of feeding our spicy foods, we can see that Bifidobacterial numbers were increased with rats in group H3 (C+ve) and group H4 (rats fed Cur) and that reached 5.98 and 6.08 log10 cells/g fecal Moreover, group rats consume black pepper and /or cumin/curcumen represents H5 and H9 groups show increases in Bifidobacterial numbers that reaches 5.12 and 5.66 log10 cells/g fecal samples. On the other hand rat groups fed orlistat (H2, C+ve), cumin (H6), curcumen/black pepper

(H7), cumin/black pepper (H8) and curcumen/black pepper/cumin (H10) were decreases at the same time point (14 days). At the end of the experiment within 28 days, it can be notice that best treated group with Bifidobacterial number is group H4 (6.19 log10 cells/g fecal samples) which fed curcumen and that was follows by groups H3, H9, H7 (6.14, 5.46 and 5.65 log10 cells/g fecal samples respectively). To conclude up, Bifidobacterial levels were increases with others spicy food consumptions especially as following H4>H3>H9>H7>H10>H8>H6.

Finally, Clostridium (His) levels have been measured and Table 5 as well representing their levels at all the time points (0, 14 and 28 days). It can be seen that Clostridium (His) numbers were at stable levels on all the time points for group H1 (C-ve) and again for group H2 (obese fed orlistat) but they were at different numbers that were 5.34 and 6.14 log10 cells/g fecal samples respectively.

Again, Clostridium show the same levels between all obese used animal models at the zero time point (mean at about 6.15 log10 cells/g fecal samples). They have been stayed at high levels at different time points especially between treated groups (H5) with BP either used alone or in combination with different spicy used foods (H7, H8 and H10). For instance, groups H8 and H10 that consuming Cu/BP and group consuming Cur/BP/Cu were at parallel ranks of His numbers (about 6.14 log10 cells/g fecal samples) at zero time point and again at day 14 of running the experimental (6.03 log10 cells/g fecal samples). However, they were declined at the 28 days to about 5.97 log10 cells/g fecal samples. To conclude up, Clostridium numbers were decreased with others spicy food consumptions especially at the end of the experimental (28 days) as following H5>H8>H10>H6>H7>H9>H4>H3.

Histopathological examination of all collected animal's organs (heart, liver and kidney):

The histopathological microscopically (H & E X 400) examination of collected liver samples, liver of rats from group 1 revealed the normal histological structure of hepatic lobule (Figure 1; L:H1). On the other hand, liver of rats from group 2 showing focal hepatocellular necrosis and apoptosis associated with mononuclear inflammatory cells infiltration (Figure 1; L:H2) in addition to liver of rats from group 3 and group 4that showed slight cytoplasmic vacuolization of hepatocytes (Figure 1; L:H3 & L:H4). The examined sections from group 5 also revealed no histopathological alterations (Figure 1; L:H5) as well as liver of rats from group 6 that showed no changes (Figure 1; L:H6). Kupffer cells activation was the only change observed in liver from group 7 (Figure 1; L:H7). However, liver of rats from group 8 showed no histopathological changes (Figure 1; L:H8). Meanwhile, liver of rats from group 9 showed focal hepatocellular necrosis associated with mononuclear inflammatory cells infiltration (Figure 1; L:H9) while examined sections from group 10 showed slight vacuolation of some hepatocytes and slight dilatation of hepatic sinusoids (Figure 1; L:H10).

Finally the histopathological examination of kidneys microscopically (H & E X 400) showing that rats group 1 has normal histology of renal tissue (Figure 1; K:H1). On the other hand, kidneys of rats from group 2 revealed congestion of renal blood vessel and kidneys sections from group 3 shown vacuolation of epithelial lining renal tubules (Figure 1; K: H2 and K: H1 respectively). However, kidneys from group 4 showed no histopathological alterations (Figure 1; K: H4). Vacuolation of epithelial lining some renal tubules was the only observed change in kidneys from group 5 (Figure 1; K: H5). Moreover, examined sections from group 6, 7 & 8 revealed no histopathological alterations (Figure 1; K:H6, K:H7 & K:H8 respectively). While sections from group 9 showed necrobiosis of epithelial lining renal tubules (Figure 1; K:H9) and sections group 10 showed no histopathological alterations (Figure 1; K:H10).

Discussion

The prevalence of obesity has dramatically worldwide increased over the past decades posing serious public health threats between all human ages and genders depending on many correlated factors. Among such factors is the dietary ones; including the types of diets with a debate optimal macronutrient composition in order to achieve the best results within body weight loss and/or management. Different used spicy foods have been shown to play a beneficial role in obesity management. Therefore, exploring the effects of certain herbs or dietary spices on obesity may be promising and/or controlling the human body weight is the main objective for this study. It aimed to study the effects of different commonly used spices mainly curcumin, black pepper, cumin either alone or in mixtures for body weight management and/or reductions in addition to the possible health benefits. Additionally, the present work was conducted to study the effect of some spices on body weight reductions and colonic microbiota interaction between obese animal models and all collected data are presented as following. The kidney and liver functions and kidney data shown the best effective levels with group H10 that were on diets added with mix of curcumin/black pepper/cumin. Indeed, [31] suggested that piperine protects the kidney against ischemia-reperfusion induced acute kidney injuries by its anti-inflammatory and anti-oxidative properties. At the same time, [32] stated that dietary cumin (1.25%) for

8 weeks lowered blood urea level and creatinine in diabetic animals. Additionally, the gut microbiota composition in association to consumed spicy foods has been measured between obese animal models in this study. The total numbers presented different correlations with special refer to the rat groups fed Cur mixed with BP (H7; mixture of both BP/Cur). It was at the end of the experimental nearly at bacterial level of the same as control positive group (H3; C+ve). The effects were seen at different groups as H4>H5>H8>H6>H10>H9. Additionally, measured Lactobacillus were at the end of the experimental with the groups that arranges as H4>H3>H7>H8>H5>H6 log10 cells/g fecal samples. Thus used BP and / or Cur shown positive effects on gut microbiota mainly the lactic acid producer bacteria (Lactobacillus) but such effect was renews by addition alone (as seen with group H10) or mixes (as seen with group H9). Moreover, Bifidobacterial levels were increases with spicy used consumptions as H4>H3>H9>H7>H10>H8>H6. On the other hand, Clostridium numbers were decreased with spicy foods at the end of the experimental as H5>H8>H10>H6>H7>H9>H4>H3. Indeed, the effects of gut microbiota on obesity previously have been found in most animal and some human studies. For example certain strains of Firmicutes, Lactobacillus, and Bacteroidetes are positively associated with obesity development, while Bifidobacterium, most Lactobacillus, and some Bacteroidetes show anti-obesity activities [33]. Moreover, Lactobacillus casei strain Shirota-containing beverage reduced body weight and increased high-density lipoprotein cholesterol level [34]. Obese mice treated with Bifidobacterium MKK4 for 8 weeks reduced body, improved levels of regulated gut microbiota dysbiosis [35]. Again, [36] suggests that consumption of milk fermented by L. fermentum improves serum lipid trends in rats by lowering serum TCHO, TG, LDL-c levels, as well as by increasing HDL-c level. It also all show to play a role in the prevention of obesity induced by a high-fat diet.

Conclusion

Several healthy added nutritional foods have promoted health benefits to the host gastrointestinal especially after consuming different mixtures of spicy foods which mainly recognized to their high content of antioxidant in association to colonic microbiota composition and activities. Consuming black pepper declined the BWG at the different levels after being added with/without mixing it with cumin or curcumin. Again, both cumin and curcumin reduced the obese rats' body weight either in their single or mixed doses but with big reduction levels. Conversely, the mixture between the spices reduced the final body weight more than used a single one. AND show to reduce obesity risk with its complications; unidentified mechanisms to be involved but further human studies in this direction are required to elucidate novel mechanisms or pathways.

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Conflict of interest
The authors declare that there is no conflict of interest.
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Author`s contributions: All authors contributed equally.

TABLE 1. Effects of different spicy supplementations on kidney and liver functions between used rats.

Animal groups	Kidney (mg/dl)		Liver (mg/dl)	
	Creatinine	Urea	ALT	AST
Non-obese **(C-ve; H1)**	0.482±0.01^{b}	24.05±0.51^{d}	66.7±0.70^{d}	41.8±0.84^{d}
Obese on Orlistat **(H2)**	0.490±0.13^{b}	24.73±1.80^{d}	67.3±2.62^{d}	43.8±2.89^{d}
Obese **ND*(C+ve; H3)**	1.62±0.04^{a}	53.05±0.52^{a}	104.8±3.37 ^{a}	105.7±0.76^{a}
Obese on **Cur; H4**	0.495±0.04^{b}	33.55±0.52^{bc}	84.7±0.70^{b}	65.8±1.74^{c}
Obese on **Bp;H5**	0.718±0.03^{b}	37.75±3.57^{b}	76.6±0.98^{c}	71.3±0.81^{b}
Obese on **Cu;H6**	0.840±0.42^{b}	37.38±3.37^{b}	78.6±2.45^{c}	70.2±0.95^{b}
Obese on **Cur/Bp;H7**	0.507±0.01^{b}	33.65±0.51^{bc}	77.4±0.29^{c}	42.1±1.38^{d}
Obese on **Cu/Bp;H8**	0.793±0.35^{b}	33.35±0.52^{bc}	69.0±0.57^{d}	61.5±0.51^{c}
Obese on **Cu/Cur;H9**	0.783±0.33^{b}	27.28±3.79^{cd}	71.3±0.88^{d}	61.9±1.01^{c}
Obese **Cur/Bp/Cu;H10**	0.503±0.01^{b}	24.55±0.51^{d}	66.6±1.30^{d}	44.0±1.56^{d}

Values are mean ± SE; n=8. Means under the same column being different superscript letters are different significantly *(P<0.05)*. * ND means that group rats fed on normal diet.

TABLE 2. Total gut microbiota population measured affected by different spicy foods supplementation between used animal models.

Groups	Hours (h; lag_{10} Total cells/g collected fecal samples)			Mean[2]
	0	14	28	
Non-obese **(C-ve; H1)**	16.08±0.01	16.15±0.00	16.13±0.03	16.12^{b}±0.03
Obese on Orlistat **(H2)**	16.12±0.02	16.03±0.06	16.09±0.03	16.08^{b}±0.07
Obese **ND*(C+ve; H3)**	16.02±0.06	15.07±0.04	15.93±0.16	15.88^{b}±0.16
Obese **Cur; H4**	15.98±0.08	15.69±0.29	15.90+0.04	15.85^{b}±0.33
Obese **Bp;H5**	15.12±0.22	15.92±0.10	15.67±0.08	15.85^{b}±0.23
Obese **Cu;H6**	16.04±0.35	15.14±0.32	15.22±0.21	15.46^{a}±0.46
Obese **Cur/Bp;H7**	16.01±0.13	15.75±0.07	16.12±0.12	15.96^{b}±0.17
Obese **Cu/Bp;H8**	16.03±0.28	15.07±0.28	15.45±0.28	15.51^{a}±0.43
Obese **Cu/Cr;H9**	16.05±0.43	15.06±0.30	15.12±0.31	15.40^{a}±0.53
Obese-**Cur/Bp/Cu;H10**	16.09±0.44	14.92±0.31	15.15±0.35	15.38^{a}±0.57
Mean[1]	16.03^{b}±0.09	15.55^{a}±0.48	15.68^{a}±0.43	

Mean[1] ± SE in the same column with different superscript letters are different significantly (***P<0.05***), Mean[2] ± SE in the same row with different superscript letters are different significantly (***P<0.05***).

TABLE 3. Gut microbiota populations (*Lactobacillus*) measured affected by different spicy foods supplementation between used animal models.

Groups	Hours (h; lag_{10} *Lactobacillus* cells/g fecal samples)			Mean[2]
	0	14	28	
Non-obese **(C-ve; H1)**	6.72±0.03	6.75±0.06	6.77±0.05	6.74^{e}±0.09
Obese on Orlistat **(H2)**	5.84±0.12	5.52±0.13	5.36±0.17	5.57^{b}±0.21
Obese **ND*(C+ve; H3)**	5.82±0.12	5.84±0.12	6.18±0.10	5.95^{c}±0.17
Obese **Cur; H4**	5.76±0.19	6.22±0.14	6.33±0.18	6.10^{d}±0.26
Obese **Bp;H5**	5.76±0.15	5.85±0.11	5.67±0.07	5.75^{b} ±0.20
Obese **Cu;H6**	5.83±0.11	5.20±0.25	5.26±0.23	5.42^{a}±0.31
Obese **Cur/Bp;H7**	5.70±0.11	5.78±0.15	6.09±0.09	5.85^{bc} ±0.19
Obese **Cu/Bp;H8**	5.84±0.06	5.71±0.03	5.76±0.07	5.76^{b}±0.10
Obese **Cu/Cr;H9**	5.89±0.05	5.72±0.04	5.71±0.16	5.80^{b}±0.16
Obese-**Cur/Bp/Cu;H10**	5.90±0.05	5.83±0.11	5.90±0.11	5.77^{b}±0.14
Mean[1]	5.90^{b}±0.30	5.83^{a}±0.40	5.89^{b}±0.45	

Mean[1] in the same column with different superscript letters are different significantly (***P<0.05***), Mean[2] in the same row with different superscript letters are different significantly (***P<0.05***).

TABLE 4. Gut microbiota populations (*Bifidobacteria*) measured affected by different spicy foods supplementation between used animal models.

Groups	Hours (h; lag_{10} Bifidobacteria cells/g fecal samples)			Mean[2]
	0	14	28	
Non-obese **(C-ve; H1)**	6.51±0.00	6.52±0.09	6.61±0.02	6.55^{g}±0.11
Obese on Orlistat **(H2)**	5.50±0.06	5.42±0.08	5.21±0.11	5.38^{bc}±0.14
Obese **ND*(C+ve; H3)**	5.60±0.18	5.98±0.14	6.14±0.15	5.90^{f}±0.24
Obese **Cur; H4**	5.56±0.20	6.08±0.21	6.19±0.18	5.94^{f}±0.29
Obese **Bp;H5**	5.55±0.16	5.12±0.18	5.13±0.09	5.26^{a}±0.23
Obese **Cu;H6**	5.55±0.19	5.14±0.19	5.22±0.06	5.30^{ab}±0.25
Obese **Cur/Bp;H7**	5.57±0.03	5.47±0.02	5.46±0.04	5.49^{d}±0.05
Obese **Cu/Bp;H8**	5.44±0.11	5.07±0.14	5.32±0.08	5.28^{a}±0.17
Obese **Cu/Cr;H9**	5.58±0.05	5.66±0.02	5.65±0.04	5.63^{e}±0.07
Obese-**Cur/Bp/Cu;H10**	5.51±0.03	5.32±0.07	5.41±0.06	5.41^{cd}±0.11
Mean[1]	5.63^{b}±0.30	5.58^{a}±0.47	5.63^{b}±0.49	

Mean[1] in the same column with different superscript letters are different significantly (***P<0.05***), Mean[2] in the same row with different superscript letters are different significantly (***P<0.05***).

TABLE 5. Gut microbiota populations (Clostridium) measured affected by different spicy foods supplementation between used animal models.

Groups	Hours (h; lag_{10} *Clostridium* cells/g fecal samples)			Mean[2]
	0	14	28	
Non-obese **(C-ve; H1)**	5.34±0.04	5.33±0.02	5.37±0.01	5.34^{a}±0.05
Obese on Orlistat **(H2)**	6.15±0.02	6.13±0.01	6.15±0.02	6.14^{g}±0.03
Obese **ND*(C+ve; H3)**	6.13±0.21	5.49±0.22	5.45±0.22	5.69^{b}±0.33
Obese **Cur; H4**	6.19±0.19	5.69±0.19	5.58±0.17	5.82^{c}±0.28
Obese **Bp;H5**	6.15±0.04	5.98±0.04	5.85±0.01	6.10^{g}±0.06
Obese **Cu;H6**	6.15±0.09	5.99±0.08	5.86±0.07	5.99^{e}±0.12
Obese **Cur/Bp;H7**	6.16±0.15	5.82±0.17	5.62±0.15	5.86^{d}±0.24
Obese **Cu/Bp;H8**	6.15±0.03	6.02±0.06	5.99±0.04	6.05^{f}±0.080
Obese **Cu/Cr;H9**	6.14±0.18	5.98±0.16	5.61±0.13	5.90^{d}±0.24
Obese-**Cur/Bp/Cu;H10**	6.12±0.05	6.04±0.03	5.96±0.04	6.04^{ef}±0.08
Mean[1]	6.07^{c}±0.25	5.85^{b}±0.26	5.76^{a}±0.26	

Mean[1] in the same column with different superscript letters are different significantly ***(P<0.05)***, Mean[2] in the same row with different superscript letters are different significantly ***(P<0.05)***,

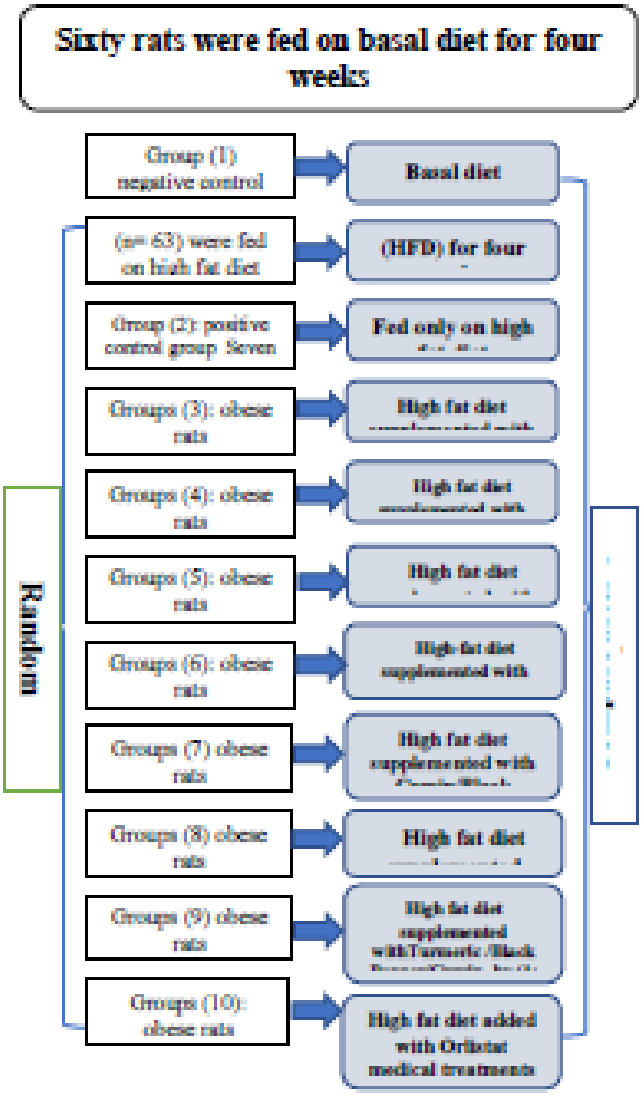

Diagram 1. Experimentaldesign

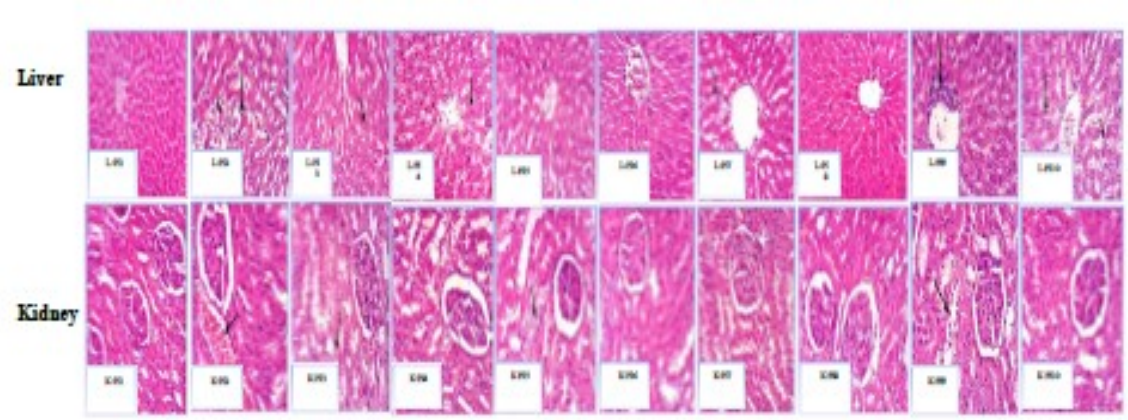

Fig.1. Liver and Kidney histological structure (H & E X 400) of different rat groups (H1:H10) fed different spicy samples. H1

(C-ve; control non-obese), H2:H10 corresponding to obese group rats fed Orlistat, control on basil diet (C+ve), Cur, Bp , Cu then mixed of Cur/Bp, Cu/Bp, Cu/Cr, and Cur/Bp/Cu respectively. L letter in each photo within the first row's photos mean samples obtained from livers and finally, K in the last row means the samples collected from Kidney while H in both rows means the experimental animal groups.

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التأثيرات الوقائية للكركمين والفلفل الأسود والكمون على وظائف الكبد والكلى بالاشتراك مع ميكروبات الأمعاء بين نماذج الحيوانات التي تعاني من زيادة الوزن

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الملخص

استهدفت الدراسة الحالية إلى قياس التأثير الوقائي للأطعمة الحارة؛ الكركمين والفلفل الأسود والكمون على وظائف الكبد والكلى بالاشتراك مع تركيبات ميكروبات الأمعاء القولونية بين نماذج الحيوانات التي تعاني من زيادة الوزن. تم استخدام عشر مجموعات من الفئران البيضاء مختلفة على النحو التالي: H1؛ المجموعة الضابطة (C-ve) لا تحتوى أدوات تجميل طبيعية من الريحان، H2؛ تحتوى على الريحان مضاف إليها باسم أورليستات كعلاج طبي لفقدان وزن الجسم، H3؛ البدينة على مستحضرات من الريحان فقط ((C+ve، H4؛ الفئران البدينة التي تم إعطاؤها الكركمين؛ (الكركم؛ 2 جم/كجم من وزن الجسم لدى الأوزان)، H5؛ تلقت الفئران البدينة الفلفل الأسود (Bp؛ 20 مجم/كجم أو 0.02 جم/كجم)، H6؛ الكمون (Cu؛ 3 مج/كجم أو 0.003 جم/كجم)، H7؛ مزيجًا من الكركمين: فلفل أسود بنسبة 1:0.01٪، H8؛ مصنوعة من الكمون/الفلفل الأسود بنسبة 1:0.01٪، H9؛ من الكمون + الكركمين بنسبة 1: 0.01٪، H10؛ من جميع الكركمين: الفلفل الأسود: الكمون (1: 0.01: 1٪).

و تستهدف الدراسة تأثير هذة التركيبات على ميكروبات الأمعاء القولونية (العصية اللبنية، بكتيريا البيفيدوباكتيريا، المطثية، والبكتيريا الكلية) داخل عينات البراز المجمعة بعد صفروي14 و28 يوم على وظائف الكبد والكلى في المصل المجمع بواسطة ألانين أمينوترانسفير أمينوترانسفيراز(AST) و اليوريا وحمض البوليك والكرياتينين بالإضافة إلى تحليل نسيج الكلى والكبد ALT و ASTمستويات وتحسنت بشكل ملحوظ مع النماذج التي تغذت على خليط من .Cur / BP / Cu (H10) كما انخفضت اليوريا بشكل ملحوظ مع H9 و H10 فى التي تغذت على / Cu) Cur و Cur / BP / Cu أى من مجموعات(فى على التوالي بينما لم يكن للكرياتينين اختلافات كبيرة بين جميع المجموعات. كشفت عينات الكبد النسيجية عن نخر الخلايا الكبدية البؤري وموت الخلايا المبرمج فيH2 ، وتجويف سيتوبلازمي طفيف للخلايا الكبدية فيH3 فى H4 بينما أظهرت H9 نخرًا بؤريًا للخلايا الكبدية مرتبطًا بتسلل الخلايا الالتهابية وحيدة النواة مقابل H10 عند التجويفات الطفيفة لبعض الخلايا الكبدية وتوسع طفيف في الجيوب الأنفية الكبدية. أظهرت الكلى مجهريًا احتقان الأوعية الدموية الكلوية ومقاطع الكلى (H2) وتجويف مقاطع الأنابيب الكلوية المبطنة للبطانة الظهارية (H3) بينما أظهرت H9 نخرًا حيويًا للأنابيب المواد المعدلة وراثيًا بمجموعات الفئران التي تغذت على خليط Cur / BP (H7) وهي نفس المجموعة الضابطة الإيجابية تقريبًاH3) ؛ (C + ve بالإضافة إلى مجموعات مختلفة مرتبة .Lactobacillus H4> H3> H7> H8> كانت H4> H5> H8> H6> H10> H9 خلية / جرام من عينات البراز بينما زادت Bifidobacterial مع استهلاك الطعام مثل H4> H3> H5> H6 log10 من ناحية أخرى، انخفضت أعداد Clostridium في نهاية التجربة مثل H5> H8> H6. H9> H7> H10> H8> وبالتالي فإن مخاليط Cur/Bp و Cur/Bp/Cu لها تأثيرات إيجابية على H10> H6> H7> H9> H4> H3. Bifidobacteria و Lactobacillus بينما انخفضت أعداد سلبًا. وفي الختام تشير الدراسة إلى أن تعزيز الفوائد الصحية سيكون أكثر قيمة مما يؤدي إلى تحسن كبير في وظائف الكبد والكلى بين النماذج البدينة، ومع ذلك، هناك حاجة إلى مزيد من الدراسات البشرية لتوضيح الآليات أو المسارات الجديدة.