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UTILITY OF 3-HYDROXY-2-(2-METHOXYPHENYL)-4H-CHROMEN-4-ONE AS ANTIOXIDANT FEED SUPPLEMENT ON MILK PRODUCTION AND GROWTH RATE IN GOATS

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ABSTRACT

The study aimed to investigate the effect of 3-Hydroxy-2-(2-methoxyphenyl)-4H-chromen-4-one / (2'-methoxy flavonol, 4) on oxidative stresses, milk production and growth rate of Zaraibi goats, compared to the standard antioxidant vitamin C. The 2'-methoxy flavonol (4) has been synthesized throughout the oxidative cyclization of 1-(2'-Hydroxyphenyl)-3-(2-methoxyphenyl) prop-2-en-1-one 3, the structure of **3** & **4** have been characterized by melting points (mp), and the spectroscopic tools. The total antioxidant capacity (TAC) of compounds **3** & **4** has been measured using the phosphomolybdenum assay.

Twenty-four pregnant Zaraibi goats were randomly distributed into three groups. The control group (CG) received the basal diet (BD), the flavonoid group (FG) received the BD plus (60 mg/kg body weight/d) of 4, and the ascorbic acid group (AAG) received the BD plus (60 mg/kg body weight/d) of vitamin C.

The results indicated that the two synthesized compounds **3** & **4** have good antioxidant capacity. The daily milk yield (DMY), milk fat content, and the average daily weight gain (DWG) of goats' kids of FG increased significantly compared to the CG and AAG groups. The results also indicated that all blood parameters were within the normal range. In conclusion, the use of the 2'-methoxy flavonol 4 as antioxidant feed supplement in the diet of pregnant Zaraibi goats can reduce the oxidative stresses, increase the daily milk yield, the milk fat percentage, and increase the average daily weight gain of goats' kids without any adverse effect on the nutritional and physiological status of animals.

Keywords: 2'-methoxy flavonol; Zaraibi goats; oxidative stress; milk production; kids' growth performance.

INTRODUCTION

The synthetic flavonol 3-Hydroxy-2-(2-methoxyphenyl)-4H-chromen-4-one / 2'-methoxy flavonol **4** is a 2-arylbenzo-pyrane (chromone) derivative Grotewold (2006). In general, the family of chromones can be easily synthesized throughout oxidative cyclization of 2'-hydroxychalcones (Prakash *et al.,* 2008; Sheng *et al.,* 2009). They are widely distributed in vegetables, fruits, seeds, nuts, and beverages. Flavonoids possess a

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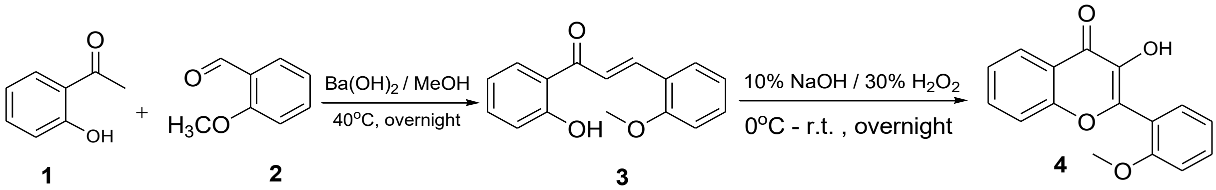
wide spectrum of pharmaceutical and biological activities, including antioxidant (Murti *et al.,* 2013), antimicrobial (Dofe *et al.,* 2017), anti-inflammatory (Li *et al.,* 2023), and antifungal activities (Prakash *et al.,* 2008).

It was found that using flavonoids as feed additives to ruminant animals' diet increased the feed intake, enhanced the digestion of nutrients, the digestion of crude fibers and cellulose degradation (Li *et al.,* 2017), reduced methane gas emission to a metabolic rate (Oskoueian *et al.,* 2013), increased the daily weight gain and growth rate of kids (Muqier *et al.,* 2017; Yaseen *et al.,* 2022).

During pregnancy, parturition, suckling, and lactation periods, ruminant, especially dairy Zaraibi goats, expose to high oxidative stress (Huang *et al.,* 2021) because of the increased nutrition and energy demand for foetus growth and development. Oxidative stress is implicated in almost all pregnancy related problems (Hussain *et al.,* 2021), which adversely affects the reproductive and productive performance of the herd. Moreover, increasing the milk yield of Zaraibi goats and enhancing the milk composition to produce a robust kid at weaning is an important issue. Due to the abilities of antioxidants to reduce the oxidative stress and overcome the pregnancy, parturition, and lactation related problems, and enhancing milk yield and composition, antioxidants are considered essential feed supplements during these critical periods (Mistry & Williams 2011; Sebastiani *et al.,* 2022).

The benefits of flavonoids, in addition to the easy and the economical efficient synthesis of this family of chromones and as a continuation of our on-going research in the synthesis of biologically active heterocyclic compounds (Ali *et al.*, 2023; El-Kady *et al.*, 2016; Halim *et al.*, 2024; Ismail *et al.*, 2021; Khlosy *et al.*, 2020; Madkour *et al.*, 2018a; Madkour *et al.*, 2018b; Mohamed *et al.*, 2020; Salem *et al.*, 2020; Salem & Errayes, 2016) encourage us to investigate the effects of the 2'-methoxy flavonol 4 on the oxidative stress, milk production, milk composition, growth rate of goats' kids, and some blood parameters of Zaraibi goats.



Scheme 1: Synthesis of 1-(2'-Hydroxyphenyl)-3-(2-methoxyphenyl) prop-2-en-1-one **3** and 3-Hydroxy-2-(2-methoxyphenyl)-4H-chromen-4-one **4**

MATERIALS AND METHODS

Chemistry

Gallenkamp electric melting point device has been used to measure the melting points which remain uncorrected. The infrared spectrophotometer Pye Unicam SP-3-300 has been used to record the infrared (IR) spectra using KBr disks. ^{1}H-NMR spectra were obtained at 300 MHz on a Varian Mercury 300BB spectrophotometer using tetramethyl silane (TMS) as internal standard in deuterated dimethyl sulfoxide DMSO and the chemical shift (δ) were reported in ppm and the coupling constant (*J*) in Hertz. Thin layer chromatography (TLC) has been used to check the progress of reactions using Merk Kiasel gel 60 F254 aluminium packed plates and spots were visualized under the UV irradiation at 254-365 nm. The spectroscopic analyses have been implemented at the Micro Analytical Centre, Cairo University, Giza, Egypt.

Synthesis of the 2'-hydroxychalcone 3

Mixture of 2'-hydroxyacetophenone 1 (10 mmol, 1.2 ml), o-anisaldehyde 2 (10 mmol, 1.2 ml), and Ba $(OH)_2$ (10 mmol, 3.15 g) in MeOH (30 mL) was stirred for 12 hr (overnight) at 40°C (Chiruta et al., 2012). Methanol was distilled off and the residue was diluted with H_2O, neutralized with HCl (1.0 N), collected with filtration, and washed with water (scheme 1). The solid product was recrystallized from petroleum ether to obtain 1-(2'-Hydroxyphenyl)-3-(2-methoxyphenyl) prop-2-en-1-one 3 as yellow crystals, in 98% yield, mp 111-111.5°C (Lit. mp 101-103°C) (Kralj *et al.,* 2013). IR (KBr) υ (cm^{-1}): 3432 (OH), 3072, 3021 (CH-aromatic), 2962, 2925 (CH-aliphatic), 1639 (C=O), 1576 (C=C).^{1}HNMR (300 MHz, DMSO-d_6): δ 12.51 (s, 1H, OH, exchangeable with D_2O), 8.20 - 8.13 (d, 2H, olefinic, *J*= 21.0 Hz), 8.00 - 6.98 (m, 8H, Ar-H), 3.91 (s, 3H, OCH_3).

Synthesis of the 2'-methoxy flavonol 4

To a well stirred and cold 0 °C solution of **3** (10 mmol, 2.54 g) in methanol (50 mL), NaOH (20 mL, 10% w/v) was added, followed by H_2O_2 (12 mL, 30%) dropwise. The reaction mixture was stirred for 3hr at 0 °C, then the ice bath was left in place, but stirring was continued overnight (Chiruta *et al.,* 2012; Shen *et al.,* 2017). The reaction mixture was poured into crushed ice and neutralized with (2M) HCl. The formed solid product was filtered off, washed with water and recrystallized from ethanol to obtain the 3-hydroxy-2-(2-methoxyphenyl)-4H-chromen-4-one 4 as pale-yellow crystals in 53.8% yield, mp 199-201 °C (Lit. mp 192-194 °C) (Frimayanti *et al.,* 2023) (scheme 1). IR (KBr) υ (cm^{-1}): 3289 (OH), 3066 (CH-aromatic), 2921 (CH-aliphatic), 1614 (C=O). ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.88 (s, 1H, OH, exchangeable with D_2O), 8.16-7.05 (m, 8H, Ar-H), 3.79 (s, 3H, OCH_3). MS *m/z* (%): 268 ($M^{\cdot+}$, 100.0), 237 (26.0), 121 (48.4), 77 (4.1).

In vitro determination of the Total Antioxidant Capacity (TAC) of the synthesized compounds

The measurements of total antioxidant capacity (TAC) of the synthesized 2'-hydroxychalcone **3** and 2'-methoxy flavonol 4 have been implemented in the laboratory of medicinal chemistry, Theodor Bilharz Research Institute, Ministry of Health and Population, Giza, Egypt. Using the UV-Vis spectrophotometer Spectronic 601 (Milton Roy, USA), the antioxidant capacity of each compound has been measured according to the phosphomolybdenum assay, with ascorbic acid as a standard antioxidant (Prieto *et al.,* 1999). In phosphomolybdenum assay reduction of Mo (VI) to Mo (V) takes place by the sample analyze to form a green complex of phosphate=Mo (V) with the maximal absorption at 695 nm in acidic medium. The procedure of the phosphomolybdenum assay has been described previously in details (Ghareeb *et al.,* 2018a; Ghareeb *et al.,* 2018b; Ghareeb *et al.,* 2018c; Sobeh *et al.,* 2018). The total antioxidant capacity has been expressed as the number of ascorbic acid equivalent (AAE).

Animal production

Animals' management and Feeding

The experiment was carried out at Sakha experimental station, Animal Production Research Institute, Kafer El-sheikh governorate, Egypt. Twenty-four pregnant Zaraibi goats (average body weight: 30.2 ± 0.65 Kg, at the age of 2-3 years, and in the first parity) at the late stage of gestation period (last month of pregnancy), were randomly distributed into three groups (8 does in each group) and kept in collective pens. Does in the control group CG fed the basal ration (BR) (70% CFM + 30 % green berseem) according to the feeding system of the experimental station, does in the flavonoid group FG received the BR plus (60 mg/Kg body weight/day) of the 2'-methoxy flavonol 4, while does in vitamin C (Ascorbic acid) group AAG received the BR plus (60 mg/Kg body weight/day) of vitamin C. Doses were administered orally as pills once daily at 9.00 am. All does in the three groups were free to drink water and given the NRC feed requirements (NRC, 2007) for pregnant and lactating goats. The experiment lasted 90 days, from the last month of pregnancy till the end of the suckling period.

Blood Sampling and analysis

5 mL blood samples have been withdrawn from the jugular veins on days 0, 30, 60, and 90 of supplementation. Blood samples were centrifuged at 3000 r.p.m. for 15 min., serum was collected in dry and clean vials and stored at -20 °C for further analysis.

Blood serum was analyzed colorimetrically by commercial kits for total protein (TP), albumin, creatinine, blood urea nitrogen (BUN) concentrations, and for Alanine amino transferase (ALT) and Aspartate amino transferase (AST) activities.
Serum was analyzed also for free radicals / lipid peroxidation represented by malondialdehyde (MDA) (Ohkawa *et al.,* 1975) and antioxidants represented by the total antioxidant capacity (TAC) (Koracevic *et al.,* 2001).

Milk sampling and analysis

Milk yield was individually measured once weekly and recorded. The measurements of the milk yields started a week after kidding till the 8th week of suckling period. Milk samples (100 mL) were collected biweekly at W_2, W_4 and W_6 of the suckling period and analyzed for milk fat, protein, lactose, total solids (TS), and solids-not-fats (SNF) % using the Lacto-scan apparatus SLP (Bulgaria). For determination of milk somatic cell counts (SCC) milk samples were collected at the middle of the experimental time (on 45th day) and analyzed using the somatic cell counter Nucleocounter SCC-100 (Chemo metric Nucleocounter family, Denmark).

Kids' performance

All does in the three groups labored normally. Kids were weighed at birth (BW), then at two months of age to determine the weaning weight (WW), and the daily weight gain (DWG) was calculated.

Statistical analysis

All data of total antioxidant capacity (TAC) of the synthesized compounds were presented as mean ± SD using SPSS 13.0 program. The statistical package SAS (SAS, 2002) was utilized to test the significance of the studied fixed effects; treatment, time of measurements, and the interaction between them on milk yield, milk composition, somatic cells count, serum TAC, MDA, and blood serum parameters using the following model.

$X_{ijk} = \mu + N_i + T_j + (N^* T)_{ij} + e_{ijk}$

Where:

X_{ijk} = the measurements of milk (yield, components, and somatic cell counts) and blood serum (parameters, TAC, and MDA) that have been measured by ith treatment and jth time of measurement,

μ = population mean,

N_i= the fixed effect of ith treatment where i = from 1 to 3, where 1 = (control), 2 = (60 mg/kg of body weight/d of 2'-methoxy favonol 4), and 3 = (60mg/ kg of body weight/d of vitamin C),

T_j = the fixed effect of jth time of measurements where j = from 1 to 4, where 1= (zero time), 2 = (30th day of supplementation), 3 = (60th day of supplementation), and 4 = (90th day of supplementation),

$(N^*T)_{ij}$ = the effect of interaction between N_i and T_j, and

e_{ijk} = the effect of random error.

RESULTS

Chemistry

Clasien-Schmidt condensation reaction has been used to synthesize the 2'-hydroxychalcone 3 *via* condensation between the 2'-hydroxyacetophenone 1 and o-anisaldehyde 2 under alkaline conditions. The 2'-hydroxychalcones 3 has been obtained in pure form in 98% yield, and gives a positive color test with $FeCl_3$ solution, which indicates the presence of the free phenolic hydroxyl group. The synthesis of the 2'-methoxy flavonol 4 has been carried out successfully via Algar-Flynn-Oyamada reaction, which involves the oxidative cyclization of the 2'-hydroxychalcone by hydrogen peroxide H_2O_2 in the presence of sodium hydroxide solution. The 2'-methoxy flavonol 4 was obtained in 53.8 % yield. The qualitative analysis for 4 indicates the presence of the free phenolic hydroxyl group. The purity of the synthesized compounds was established by TLC and melting points. Structures of 3 and 4 have been confirmed on the basis of the spectral data (IR, ^{1}H-NMR, and MS). The 2'-hydroxy chalcone 3 exhibited the IR absorptions characterized for phenolic-OH at (3432 cm^{-1}), carbonyl C=O at (1639 cm^{-1}), and olefinic C=C at (1576 cm^{-1}) functionalities. The ^{1}H-NMR spectra showed singlet due to phenolic–OH at δ 12.51 ppm (s, 1H, OH), one doublet due to the two olefinic protons characterized for the chalcone moiety at δ 8.20-8.13 ppm (d, 2H, olefinic), and multiplet due to aromatic protons at δ 8.00 - 6.98 ppm (m, Ar-H). While, the IR spectrum of the 2'-methoxy flavonol 4 showed absorption of phenolic–OH at (3289 cm^{-1}), carbonyl C=O at (1614 cm^{-1}). The ^{1}H-NMR spectra showed singlet due to phenolic–OH at δ 8.88 ppm, and multiplet due to aromatic protons Ar-H at δ 8.16-7.05 ppm.

The antioxidant activity of the synthesized compounds (TAC)

The total antioxidant capacities (TAC) of the synthesized compounds **3** & **4** have been measured in *vitro* via the phospho-molybdenum method, using Ascorbic acid as a standard antioxidant. Results in Table (1) indicate that the 2'-hydroxy chalcone 3 and the 2'-methoxyflavonol 4 possess good antioxidant activities. TAC of the chalcone 3 was 248.00 mg AAE/g compound. Since the antioxidant active site in chalcone compounds is the chalcone moiety (α,β-unsaturated carbonyl moiety), the higher the π-electrons cloud surrounding the chalcone moiety, the higher the ability of chalcones to donate odd electrons and scavenging free radicals. The TAC of the 2'-methoxy flavonol 4 was 259.35 mg AAE/g compound. In addition to the high electron cloud, the 2'-methoxy flavonol 4 can scavenge the free radicals by donating a radical proton through the free hydroxyl group at C3 position (Sousa *et al.,* 2016).

Table 1: Total antioxidant capacity (means ±S.D) of the synthesized compounds

Compound No.	Total antioxidant capacity (mg AAE / g compound)
3	248.00±2.46
4	259.35±4.37

TAC mean = Σ TAC / n; n = 3, where (n) is the number of readings.
AAE = Ascorbic acid equivalent.

Effect of 2'-methoxy flavonol on milk yield

Table (2) shows that the effect of treatments on milk production is highly significant. The average daily milk yield (DMY) of Zaraibi goats in the 2'-methoxy flavonol supplemented group (FG) is significantly higher than the control (CG) and vitamin C (AAG) supplemented groups. The overall means of DMY are 931.6, 824.2, and 589.2 g/d, respectively for FG, AAG, and CG. The results indicated that using vitamin C as antioxidant feed supplement substantially increased the average daily milk yield of dairy Zaraibi goats, compared to the control group (CG) (824.27 *vs* 582.26). Results in Table (2) showed that the DMY in Zaraibi goats increased at the first and second weeks of the suckling period, and then decreased gradually till the end of the lactation period. The highest average DMY was recorded at the second week (the peak week). Similar results were obtained previously on the same goat breed as Mousa (1996) mentioned.

Table 2: Least square means (g/d) ± SE of daily milk yield as affected by treatment, time and the interaction between them

Time	DMY (g/d)			Overall mean
	CG	FG	AAG	
W_1	714.6 ± 48.9	1010.0 ± 66.4	837.5 ± 44.7	854.0 ± 43.8 ^{a}
W_2	810.0 ± 64.0	1095.0 ± 73.9	891.7 ± 46.8	929.7 ± 48.1 ^{a}
W_3	655.0 ± 50.3	967.0 ± 71.6	829.2 ± 24.5	817.8 ± 50.4 ^{ab}
W_4	593.8 ± 123.8	885.0 ± 33.2	875.0 ± 57.4	803.3 ± 51.6 ^{ab}
W_5	566.3 ± 154.6	910.0 ± 67.8	858.3 ± 60.8	797.7 ± 63.3 ^{ab}
W_6	506.3 ± 139.7	920.0 ± 60.9	840.0 ± 49.2	777.7 ± 65.9 ^{ab}
W_7	479.2 ± 125.4	845.0 ± 67.3	762.5 ± 70.3	686.8 ± 63.5 ^{bc}
W_8	378.0 ± 121.2	820.0 ± 174.9	700.0 ± 61.9	621.8 ± 79.8 ^{c}
Overall mean	582.3 ± 94.8 ^{c}	931.5 ± 40.3 ^{a}	824.3 ± 39.5 ^{b}	

W_{1-8} = weeks of measuring and recording the milk yield starts a week after parturition till the end of suckling period, means with different superscripts (a, b, c, ab, and bc) are significantly different at (P<0.05).

Effect of 2'-methoxy flavonol on milk components

Milk somatic cell counts (SCC) of dairy Zaraibi goats during the suckling period (early lactation) presented in Table (3). Results of milk SCC revealed that 2'-methoxy flavonol and ascorbic acid feed supplements have no influence on milk SCC of dairy Zaraibi goats. The average milk SCC of the three experimental groups CG, FG, and AAG are similar and within the normal range of dairy Zaraibi goats.

Table 3: Least square means ± SE of milk somatic cell counts (cell/ml) as affected by the treatment

Group	SCC*10^5 cell/mL
CG	3.44±0.45
FG	3.64±0.67
AAG	4.24±0.90

Results in Table (4) indicated that at the second week of the suckling period, the 2'-methoxy flavonol treatment has a significant influence on milk fat% of dairy Zaraibi goats. Dams in FG have milk fat% significantly higher (P<0.05) than the CG. While milk fat% of AAG did not significantly differ than the other groups (FG and CG). At the 4th and 6th weeks of the suckling period, milk fat% of dairy Zaraibi goats is not influenced by the treatment. For milk protein, lactose, TS, and SNF, the effect of flavonoids and vitamin C supplementation was not significant all over the experimental period. Results in Table (4) showed that sampling time has a significant influence on milk fat, protein, lactose, TS, and SNF. Opposite to milk lactose, milk (fat, protein, TS and SNF) decreased significantly with time. Results also indicated that using vitamin C as feed supplement in the diet of dairy Zaraibi goats insignificantly increased milk fat, protein, TS and SNF and these findings agreed with another goat species, where milk fat, protein, TS, and SNF of Agamy goats supplemented with vitamin C increased significantly (Abd-EL-Rahman *et al.,* 2015).

Effect of 2'-methoxy flavonol on BW, WW, and DWG of goats' kids

As shown in Table (5), although the average birth weight (BW) of goats' kids in CG is higher than kids in FG and AAG, their average weaning weight (WW) is lower than that of kids in FG and AAG, which means that 2'-methoxy flavonol and vitamin C feed supplements enhance the daily weight gain (DWG) of goats' kids. The average BW of kids is 3.20, 2.02, and 2.34 Kg; the average WW of kids is 6.02, 7.67, and 6.84 Kg, respectively for CG, FG, and AAG. The average daily weight gain (DWG) of kids substantially influenced by 2'-methoxy flavonol supplementation to their dams at the late stage of pregnancy and the early lactation period. Kids of 2'-methoxy flavonol supplemented group FG have DWG significantly higher (p<0.05) than CG and AAG (62.83, 31.40 & 50.40 g/d, respectively).

Table 4: Least square means ± SE of milk components (%) as affected by treatment, time and the interaction between them

Source of variation	Fat %	Protein %	Lactose %	TS %	SNF %
Treatment * time	**NS**	**NS**	**NS**	**NS**	**NS**
W_2					
CG	$5.47^b \pm 0.7$	4.31 ± 0.2	4.15 ± 0.2	14.77 ± 0.8	8.63 ± 0.5
FG	$8.13^a \pm 0.6$	3.95 ± 0.2	3.85 ± 0.2	16.76 ± 0.7	8.63 ± 0.5
AAG	$6.41^{ab} \pm 0.5$	4.20 ± 0.1	4.23 ± 0.1	15.78 ± 0.5	9.37 ± 0.4
W_4					
CG	4.26 ± 0.5	3.45 ± 0.1	5.06 ± 0.2	13.31 ± 0.8	9.06 ± 0.3
FG	3.98 ± 0.6	3.35 ± 0.1	4.92 ± 0.2	12.78 ± 0.9	8.80 ± 0.3
AAG	3.27 ± 0.5	3.41 ± 0.1	5.01 ± 0.1	12.22 ± 0.7	8.96 ± 0.3
W_6					
CG	3.87 ± 0.8	3.06 ± 0.1	4.48 ± 0.1	11.87 ± 0.9	8.00 ± 0.1
FG	3.81 ± 0.9	3.19 ± 0.2	4.67 ± 0.4	12.16 ± 1.5	8.35 ± 0.7
AAG	2.98 ± 0.1	3.17 ± 0.1	4.65 ± 0.1	11.29 ± 0.2	8.31 ± 0.2
Treatment	**NS**	**NS**	**NS**	**NS**	**NS**
CG	4.48 ± 0.4	3.58 ± 0.1	4.66 ± 0.1	13.32 ± 0.5	8.66 ± 0.2
FG	5.44 ± 0.4	3.53 ± 0.1	4.46 ± 0.1	14.05 ± 0.5	8.62 ± 0.2
AAG	4.51 ± 0.3	3.69 ± 0.1	4.63 ± 0.1	13.53 ± 0.4	9.01 ± 0.2
Sampling Time	**	*	*	*	*
W_2	$6.70^a \pm 0.3$	$4.15^a \pm 0.1$	$4.11^c \pm 0.1$	$15.84^a \pm 0.5$	$9.00^a \pm 0.2$
W_4	$3.75^b \pm 0.3$	$3.41^b \pm 0.1$	$5.00^a \pm 0.1$	$12.70^b \pm 0.4$	$8.95^a \pm 0.2$
W_6	$3.55^b \pm 0.4$	$3.14^c \pm 0.1$	$4.60^b \pm 0.1$	$11.77^b \pm 0.6$	$8.22^b \pm 0.3$

Treatment = (60 mg/kg body weight/d) of the 2'-methoxy flavonol 4 and/or vitamin C, sampling time (W_2, W_4, and W_6) the 2nd , 4th and 6th weeks of suckling period, NS = insignificant, means with different superscript (a, b, c) are significantly different at (P<0.05).

Table 5: Least square means ± SE of birth weight (Kg), weaning weight (Kg), and daily weight gain (g/d) of goats' kids as affected by the treatment

group	BW (Kg)	WW(Kg)	DWG(g/d)
CG	3.20±0.37	6.02±0.79	31.40 ± 8.34^b
FG	2.03±0.34	7.67±0.73	62.83 ± 7.61^a
AAG	2.34± 0.37	6.84±0.79	50.40 ± 8.34^{ab}

BW= birth weight, WW= weaning weight, and DWG= daily weight gain, means with different superscripts (a, b, ab) are significantly different at (P<0.05).

Effect of 2'-methoxy flavonol on blood parameters

Table (6) demonstrated that serum total protein (TP), albumin, globulin, creatinine, and blood urea nitrogen (BUN) concentrations and total antioxidant capacity (TAC), malondialdehyde (MDA), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) activities of dams in the three experimental groups are within the normal range of dairy Zaraibi goats. No significant differences have been observed due to supplementation with 2'-methoxy flavonol 4 and / or vitamin C on BUN, Globulin, and creatinine concentration and on TAC, MDA, and AST activities. Although 2'-methoxy flavonol 4 supplementation significantly decreased the Albumin concentration and ALT activity, their values are still within the normal range of the dairy Zaraibi goats. The results revealed also that Vitamin C supplementation increased serum TP. The above results indicated that dams in the three experimental groups are in good nutritional and physiological status, which indicates that using 2'-methoxy flavonol 4 and vitamin C as feed supplements has no negative effect on their nutritional and physiological status.

DISCUSSION

The high energy demand for foetus growth and development during pregnancy and early lactation periods induces oxidative stress, which decreases the mammary gland functions and consequently decreases the milk synthesis. Through the in *vitro* study of the antioxidant activity of the 2'-methoxy flavonol 4, we indicated that the 2'-methoxy flavonol 4 is a potent antioxidant and can scavenge free radicals. Furthermore, the in *vivo* study reported that, at 60 days of supplementation the MDA concentration in FG is lower than that in CG, and at 30 days of supplementation the TAC of FG and AAG was higher than that of the CG, which indicates in *vivo* antioxidant activity of 2'-methoxy flavonol and its ability to reduce the lipid peroxidation through direct scavenging of free radicals and consequently enhance the mammary gland functions and the milk synthesis.

Since there are no previous studies had explored the effect of synthetic flavonoids / 2'-methoxy flavonol on dairy goats' milk yield and composition and on the growth performance of goat's kids, we compared our findings with studies supplementing flavonoids from different sources and on the different species. The previous studies indicated that flavonoid extracts have the ability to increase the effective degradation rate of dry matters and the utilization of nutrients, which led to increased milk production of dairy goats (Zhao *et al.,* 2022). Also, it had been indicated that flavonoids can significantly increase the cellulolytic bacteria *Ruminococcusalbus* which potentially increases cellulose degradation and subsequently increases the daily milk yield (Li *et al.,* 2020). Moreover, the antimicrobial properties of flavonoids enable them to effectively reduce the ruminal methanogens and protozoa populations, which consequently reduce the methane gas emission without any adverse effects on rumen microbial fermentation (Kim *et al.,* 2015; Oskoueian *et al.,* 2013; Sinz *et al.,* 2018). These favourable effects of flavonoids on rumen fermentation and nutrient utilization lead to the potential increase in milk production.

It had been shown previously that vitamin C supplementation can manage and reduce oxidative stress and enhance milk production of goats (Abd-EL-Rahman *et al.,* 2015; Semsirmboon *et al.,* 2023) and our findings are in line with these previous findings.

Table 6: Least square means ± SE of blood parameters as affected by treatment, time, and the interaction between them

group	0 day	30th day	60th day	90th day	Overall mean
MDA (µMol/ml)					
CG	4.72 ± 0.5	7.75 ± 1.1	7.02±0.7	6.92 ± 1.7	6.57±0.6
FG	4.45 ± 0.3	9.28 ± 1.2	5.44±0.7	6.70 ± 1.1	6.79±0.6
AAG	5.91 ± 0.7	9.30 ± 0.6	7.16±0.6	6.40 ± 0.9	7.19±0.4
Overall mean	5.03 ± 0.3[c]	8.80±0.6[a]	6.52±0.4[b]	7.04 ± 0.7[b]	
TAC (mMol/L)					
CG	0.32 ± 0.1	0.54 ± 0.1	0.43 ± 0.1	0.48 ± 0.1	0.44 ± 0.04
FG	0.33 ± 0.04	0.61 ± 0.1	0.33 ± 0.1	0.43 ± 0.1	0.43 ± 0.04
AAG	0.43 ± 0.1	0.65 ± 0.04	0.49 ± 0.04	0.42 ± 0.1	0.50 ± 0.03
Overall mean	0.36 ± 0.04[b]	0.60 ± 0.03[a]	0.42 ± 0.04[b]	0.44 ± 0.04[b]	
TP (g/dL)					
CG	7.42 ± 0.1	7.92 ± 0.4	8.19 ± 0.2	8.27 ± 0.1	7.93±0.2[ab]
FG	7.24 ± 0.3	7.84 ± 0.3	7.42 ± 0.5	7.94 ± 0.3	7.44±0.3[b]
AAG	7.73 ± 0.2	8.04 ± 0.3	8.17 ± 0.2	8.09 ± 0.3	8.01±0.1[a]
Overall mean	7.47 ± 0.1	7.95 ± 0.2	7.66 ± 0.3	8.10 ± 0.2	
Albumin (g/dL)					
CG	3.70 ± 0.1	3.73 ± 0.1	3.70 ± 0.1	3.58 ± 0.1	3.68 ± 0.03[a]
FG	3.65 ± 0.03	3.64 ± 0.04	3.57 ± 0.04	3.46 ± 0.1	3.58 ± 0.03[b]
AAG	3.73 ± 0.04	3.66 ± 0.1	3.65 ± 0.1	3.58 ± 0.1	3.65 ± 0.02[a]
Overall mean	3.69 ± 0.02[a]	3.68 ± 0.03[a]	3.64 ± 0.03[a]	3.54 ± 0.03[b]	
Globulin (g/dL)					
CG	3.72 ± 0.1	4.19 ± 0.5	4.49 ± 0.3	4.69 ± 0.1	4.26 ± 0.2
FG	3.59 ± 0.3	4.21 ± 0.3	3.84 ± 0.4	4.49 ± 0.3	3.86 ± 0.2
AAG	4.00 ± 0.2	4.38 ± 0.3	4.52 ± 0.2	4.52 ± 0.3	4.36 ± 0.1
Overall mean	3.78 ± 0.1[b]	4.27 ± 0.2[ab]	4.02 ± 0.3[ab]	4.56 ± 0.1[a]	
ALT (IU/L)					
CG	23.86 ± 0.7	27.00 ± 1.2	25.17 ± 1.1	26.00 ± 1.4	25.49 ± 0.6[a]
FG	22.75 ± 1.2	24.38 ± 0.9	24.29 ± 1.02	24.71 ± 0.9	23.99 ± 0.5[b]
AAG	25.50 ± 1.2	26.71 ± 1.1	26.00 ± 1.2	25.00 ± 0.8	26.19 ± 0.5[a]
Overall mean	24.57 ± 0.6	26.01 ± 0.6	25.16 ± 0.6	25.16 ± 0.6	
AST (IU/L)					
CG	38.00 ± 6.0	53.60 ± 2.0	58.33 ± 4.4	39.50 ± 2.6	45.56 ± 2.8
FG	45.14 ± 3.4	60.00 ± 4.7	48.57 ± 6.8	45.88 ± 5.8	50.64 ± 2.4
AAG	42.25 ± 1.9	57.57 ± 5.1	50.75 ± 4.3	42.00 ± 7.2	48.13 ± 2.4
Overall mean	40.72 ± 2.8[b]	57.17 ± 3.03[a]	52.07 ± 3.0[a]	42.50 ± 2.9[b]	
BUN (mg/dL)					
CG	46.93 ± 1.2	47.28 ± 1.8	47.06 ± 3.0	55.53 ± 2.8	49.19 ± 1.3
FG	49.22 ± 1.3	49.15 ± 2.5	48.02 ± 5.7	59.62 ± 1.8	51.94 ± 1.1
AAG	48.68 ± 1.4	48.17 ± 1.5	46.23 ± 1.5	54.48 ± 1.8	49.37 ± 1.1
Overall mean	48.29 ± 1.3[b]	48.17 ± 1.4[b]	47.05 ± 1.4[b]	57.15±1.4[a]	
Creatinine (mg/dL)					
CG	0.66 ± 0.1	1.10 ± 0.1	0.86 ± 0.1	0.97 ± 0.1	0.90 ± 0.1
FG	0.82 ± 0.1	1.15 ± 0.3	1.03 ± 0.2	0.88 ± 0.2	0.97 ± 0.1
AAG	0.78 ± 0.1	0.86 ± 0.2	0.98 ± 0.1	0.93 ± 0.1	0.89 ± 0.1
Overall mean	0.75 ± 0.1[b]	1.04 ± 0.1[a]	0.96 ± 0.1[ab]	0.93 ± 0.1[ab]	

MDA= malondialdehyde, TAC= total antioxidant capacity, TP= total protein, BUN= blood urea nitrogen, ALT= Alanine amino transferase, AST= Aspartate amino transferase, means with different superscript (a, b, ab, c) are significantly different at ($P<0.05$).

The milk fat content increases by increasing the crude fiber content in the diet of dairy animals (Abdel-Rahman & Mehaia, 1996), and as mentioned before, flavonoids have the ability to increase the degradation and utilization of crude fiber, which explains the substantial increase in milk fat % of 2'-methoxy flavonol group (FG), compared to the control (CG) and ascorbic acid group (AAG). Also, it is well known that the stage of lactation affects the milk fat content, as the lactation progresses, the milk fat content decreases (Šlyžius *et al.,* 2017). These results are consistent with that obtained by two other investigators, who indicated that flavonoid extracts from hybrid *Broussonetia papyrifera* fermented feed can increase the polyunsaturated fatty acids in goats' and cows' milk (Si *et al.,* 2018; Zhao et al., 2022). Values of milk components (fat, protein, lactose, TS, and SNF) obtained in the present study were within the normal range of dairy Zaraibi goats' milk and higher than that obtained previously on the same breed (Abdelhamid *et al.,* 2011; Abedo *et al.,* 2013; Ahmed *et al.,* 2008).

According to the study that stated "the threshold of 16,000,000 cells/ml gave the best indication for health status of the Egyptian Nubian (Zaraibi) goat breed" (El-Saied *et al.,* 2003), values of milk SCC of Zaraibi goats in the three experimental groups are within the normal range of healthy dairy Zaraibi goats. The results of the present study are close to that obtained before (Ahmed *et al.,* 2008) and extremely lower than other studies on the same goat breed (Abdelhamid *et al.,* 2011; Madkour *et al.,* 2016). On the other hand, the results of the present study disagree with that indicated alfalfa flavonoids substantially decreased milk SCC of Holstein cows (Zhan *et al.,* 2017). Our findings also disagree with the results indicated that milk SCC of Agamy goats supplemented with vitamin C is significantly lower than that of the control group (Abd-EL-Rahman *et al.,* 2015).

Since dams' milk is the sole source of food to the per-weaned kids, the higher the quantity and quality of milk suckled the higher the average daily weight gain of the kids. The substantial increase in the average DWG of kids, whose dams supplemented with 2'-methoxy flavonol indicates the increase in the average DMY and in the milk fat%. Also, it was previously indicated that feed supplements rich in flavonoids increased the birth weight and daily weight gain, and decreased the mortality rate of Beetal goats' kids reared under a sub-tropical environment (Yaseen *et al.,* 2022). Moreover, it was indicated that flavonoids significantly increased the daily weight gain and the average daily feed intake, and significantly decrease the feed conversion ratio of meat sheep (Muqier *et al.,* 2017). All these findings are considered a well explanation for the substantial increase in the daily weight gain of kids whom dams have been supplemented with 2'-methoxy flavonol 4. The increase in average DWG of kids that their dams supplemented with vitamin C can be supported by the study, which indicated that vitamin C supplementation significantly increased the weaning weight as well as the daily weight gain of kids in the vitamin C supplemented group (Abd-EL-Rahman *et al.,* 2015).

Our findings indicated also that all measured biochemical parameters are within the normal range of dairy Zaraibi goats and similar to that obtained previously on the same breed (Abdelhamid *et al.,* 2011; Abou-Elenin *et al.,* 2016; Ahmed *et al.,* 2008), and are similar also to that obtained on different goat breeds (Tibbo *et al.,* 2008).

CONCLUSION

Results showed that the use of 2'-methoxy flavonol 4 as antioxidant feed supplements in the diet of pregnant Zaraibi goats at the late stage of pregnancy and early lactation periods can significantly increase the daily milk yield, milk fat %, and the daily weight gain of kids, without any adverse effect on the nutritional and physiological status of goats.

Statements & Declarations

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No funding was received for conducting this study.

Declaration of competing interest

There are no conflicts of interest to declare.

Data availability

All data supporting the results of this study are within the manuscript.

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إستخدام ٣-هيدروكسي-٢-(٢-ميثوكسي فينيل)-٤ هيدرو-كرومين-٤-اون كإضافات غذائية مضادة للاكسدة على إنتاج الحليب ومعدل النمو في الماعز

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تهدف هذه الدراسة إلى دراسة تأثير إستخدام ٣-هيدروكسي-٢-(٢-ميثوكسي فينيل)-٤H-كرومين-٤-اون / (٢'-ميثوكسي فلافونول) (٤) و هو احد مشتقات الفلافونيدات المصنعة معمليا كمكمل غذائي مضاد للاكسدة على الإجهاد التأكسدي، وإنتاج الحليب، ومعدل نمو الجداء في الماعز الزرايبي، مقارنةً بفيتامين سي كمضاد للأكسدة قياسي. تم تحضير ٢'-ميثوكسي فلافونول (٤)، من خلال تفاعل التأكسد الحلقي لـ ١-(٢'-هيدروكسي فينيل)-٣-(٢-ميثوكسي فينيل) بروب-٢-إين-١-أون(٣) وهو احد مشتقات الشالكونيدات وتم التاكد من التركيب الكيميائي للمركبين (٣ و٤) من خلال قياس درجات الانصهار (mp) والأدوات الطيفية (مثل الأشعة تحت الحمراء والرنين النووي المغناطيسي البروتوني والطيف الكتلي). كما تم قياس السعة الكلية المضادة للأكسدة (TAC) للمركبين (٣ و٤) باستخدام اختبار الفوسفوموليبدينوم.
تم توزيع أربع وعشرين ماعزًا عشار في الشهر الاخير من فترة الحمل من سلالة الزرايبي عشوائيًا على ثلاث مجموعات. تلقت المجموعة الكنترول (CG) النظام الغذائي الأساسي (BD)، بينما تلقت مجموعة الفلافونيدات (FG) النظام الغذائي الأساسي بإضافة إلي (٦٠ ملجم/كجم من وزن الجسم/ يوم) من المركب رقم ٤ (٢'-ميثوكسي فلافونول)، بينما تلقت مجموعة فيتامين سي (AAG) النظام الغذائي الأساسي بإضافة إلي (٦٠ ملجم/كجم من وزن الجسم/ يوم) من فيتامين سي.
أشارت النتائج إلى أن المركبين المُصنّعين (٣ و٤) يتمتعان بقدرة جيدة على مقاومة الأكسدة. وقد زاد معدل إنتاج اللبن اليومي (DMY)، ومحتوى اللبن من الدهن ، ومعدل الزيادة اليومية في وزن الجداء (DWG) في المجموعة FG بشكل ملحوظ مقارنةً بمجموعتي CG وAAG. كما أشارت النتائج إلى أن جميع قياسات الدم التي تم قياسها تقع ضمن المعدلات الطبيعية. ختامًا، يمكن أن يُقلل استخدام ٢'-ميثوكسي فلافونول(٤) كمكمل غذائي مضاد للأكسدة في تغذية الماعز الزرايبي العشار من الإجهاد التأكسدي، ويزيد من إنتاج الحليب اليومي ونسبة دهن الحليب، ويزيد من معدل الزيادة اليومية في وزن الجداء دون أي تأثير سلبي على الحالة الغذائية والفسيولوجية للماعز.