Bioactivity of Some Natural and Semisynthetic Coumarin Derived Compounds

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Abstract

A couple of natural coumarins was identified in the seeds of two apples' cultivars commonly known as Granny Smith and Red Delicious. The effect of the phenolic hydroxyl moieties found in these products was evaluated on the bioactivity. This evaluation included the structural alteration of these moieties into less hydrophilic ones to explore the significance of the parent moieties on the biological activity. The investigated biopotentials were antioxidant, antiproliferative, antibacterial, and antifungal effects. The antioxidant potential was investigated by detecting the ability of the natural and semisynthetic coumarins to trap the free hydroxyl and DPPH radicals. The antiproliferative potential was assessed via an MTT-depended assay versus eight cancerous-cell lines, included HeLa, SK-OV-3, AR42J, MCF-7, AB12, KYSE-30, LC540, and AMN3. The antibacterial potential was tested versus six common pathogenic bacterial strains via a well-defined disc diffusion assay. These pathogens were Escherichia coli, Salmonella typhi, Klebsiella pneumonia, Haemophilus influenzae, Shigella dysenteriae, and Pseudomonas aeruginosa. The antifungal potential was also screened by utilizing a similar microbiological technique versus three pathogenic fungi, involved Candida albicans, Aspergillus flavus, and Aspergillus niger. It is concluded that the investigated chemical moiety has a positive influence on the antioxidant and antiproliferative potentials of the natural derivatives, and a negative one on their antibacterial and antifungal potentials.

Key Words: Natural and Semisynthetic Coumarins, Biological Activity, Phenolic Hydroxyl Moiety, Structural Alteration.

DOI Number: 10.14704/nq.2021.19.6.NQ21078 **NeuroQuantology 2021; 19(6):129-138**

Introduction

From ancient times to date, nature constitutes the main source of the biochemical agents which possess multifarious biological-biased activity owing to their variation in the chemical characteristics and targeted biomolecules (Oglah and Mustafa, 2020a, 2020b). Exploring the chemical structures of the isolated natural products and investigating their valuable pharmacological activities may accelerate the progress of the drug innovation process (Moath Kahtan Bashir et al., 2020; Mustafa et al., 2020a; Oglah et al., 2020b).

Products inspired by nature and based in their chemical structures on coumarin backbone have magnetized a senior attention, part of which has directed toward the exploration of their biomedical activities (A.M. Nejres et al., 2020; Aws Maseer Nejres et al., 2020). Models of these actions include the antibacterial (Mustafa et al., 2020b), antifungal (Medimagh-Saidana et al., 2015; Mustafa et al., 2021a, 2021b; Mustafa and Abdulaziz, 2021a, 2021b, 2020), antioxidant (Mustafa et al., 2020c), anticancer (Moath Khtan Bashir et al., 2020; Mustafa, 2019; Mustafa et al., 2020d), anticholinesterase (Mahmood et al., 2014), and anticonvulsant (Asif and Imran, 2019) effects.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 05 April 2021 **Accepted:** 20 May 2021

Natural coumarin-based derivatives can be isolated from many sources including plant realm, in which, these derivatives have publicized in various plant parts (Bashir et al., 2021; Kummerle et al., 2018). Structural modification of bioactive agents may afford many auxiliary applications (Mao et al., 2016; Mustafa et al., 2021d). Examples include scouting the biotargets, modes of action, and binding interactions of novel agents. Defeating the multi-drug resistance of agents with antimicrobial or antitumor activity. Repurposing of currently marketed drugs, modulating their metabolic fates, and pharmacokinetic parameters. Simplifying the complex structures of agents with high-molecular weights to afford simpler molecules having the similar bioactivity and being easily synthesized (Mustafa, 2021; Mustafa et al., 2021c; Yao et al., 2017).

For natural products, the eventual target of structural modification is to optimize their drug-like properties. This modification may manifest by removing, adding, or replacing the original functional groups to evaluate their impact on the biomedical and biophysicochemical properties (Li and Lou, 2018). The phenolic hydroxyl group included in the chemical structures of many natural pharmacophores may handle a charming influence on the aforementioned properties (Huffman and Shenvi, 2019).

The study targets to investigate the impact of the phenolic hydroxyl groups included in the chemical structures of two natural coumarins, which have previously isolated from the seeds of two apples' cultivars named Red Delicious and Granny Smith. This investigation has carried out by chemically modifying these functional groups to less hydrophilic moieties. The estimated biological activities include antioxidant, antiproliferative, antibacterial, and antifungal effects.

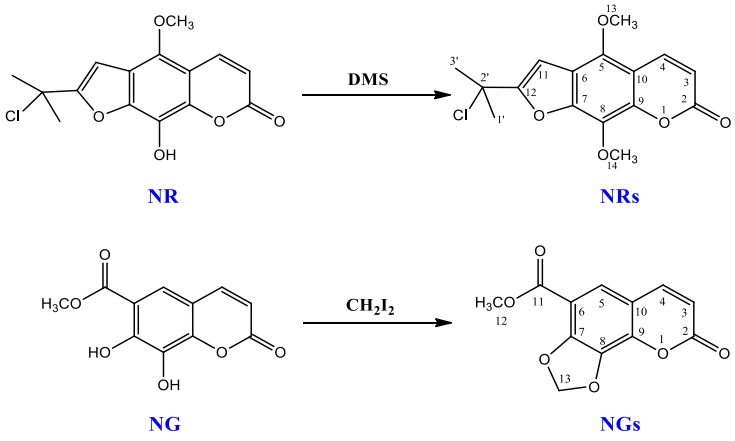
Experimental Work

Material and Methods

Human cancer cell lines, reagents, and chemicals appointed for this study have obtained from documented international suppliers named Sigma-Aldrich, CHEM-LAB, Scharlau, Bio-World, Haihang, and others. Thin-layer chromatography (TLC) has engaged by eluting the spots seeded on silica gel GF_{254} (type 60) plates with a mixture of CH_2Cl_2: EtOH (3:1). The melting points (m.p.) of the semisynthetic coumarins have recorded on electrochemical CIA 9300 equipment via an open-capillary style. The foundation of specific functional were inspected by analyzing the FTIR spectra of these products acquired from Bruker-Alpha ATR spectroscopy. UVD-2950 (LABOMED) apparatus was employed to detect the maximum absorptions (λ_{max}) of the natural and semisynthetic coumarins at the ranges of ultraviolet and visible wavelengths. The chemical structures of the semisynthetic coumarins were established by studying their ^{13}C-NMR (75 MHz) and ^{1}H-NMR (300 MHz) spectra recorded by Bruker 300 MHz AVANCE III HD NMR Spectroscopy.

Synthesis of the Semisynthetic Coumarins

The facile synthesis of the semisynthetic coumarins (**NRs** and **NGs**) from their corresponding natural precursors (**NR** and **NG**) has illustrated in Scheme 1.



NR: Natural coumarin isolated from the seeds of Red Delicious apple
NG: Natural coumarin isolated from the seeds of Granny Smith apple

Scheme 1. The synthesis of the semisynthetic coumarins from their corresponding precursors

*Synthesis of 2-(2-chloropropan-2-yl)-4,9-dimethoxy-7H-furo[3,2-g]chromen-7-one (**NRs**)*

The mixture of **NR** (0.554 g, 1.8 mmol) and dry potassium carbonate (0.5 g, 3.6 mmol) has blended for 30 min in a solvent-free medium utilizing mortar and pestle. The resulted blend has tempered by heating at 70°C for 1 hr and diluted minutely with dry ethyl acetate. The mixture of dimethyl sulfate (0.2 ml, 2 mmol, DMS) in 10 ml dry ethyl acetate has prepared and stepwise added to the first mixture. The reaction mixture has refluxed for 3 hr under dry circumstances and then filtered. The acquired filtrate has washed with H_2O, and the separated organic layer condensed under vacuum. The residue has poured into a mixture of powdered ice and H_2O. Upon filtration, the solid was washed with cold H_2O and recrystallized from an ether: EtOH (2:1) mixture (Mustafa et al., 2018).

NRs: Yellow powder; m.p.=189-192°C; λ_{max} (EtOH)=318 nm; R_f =0.72; % yield=71.89 (0.414 g); FTIR (ν, stretching, cm^{-1}): 3094, 3054 (=C-H), 2892 (C-H, alkyl), 1733 (C=O, ester), 1632, 1590 (C=C), 1554 (C=C, aromatic), 1250, 1050 (C-O-C, alkyl-aryl ether), 734 (C-Cl); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ= 8.08 (1H, d, *J*= 9 Hz, H-4), 6.70 (1H, s, H-11), 6.22 (1H, d, *J*= 9 Hz, H-3), 4.35 (6H, s, H-13, H-14), 2.01 (6H, s, H-1', H-3') ppm; ^{13}C-NMR (DMSO-d_6, 75 MHz): δ= 160.8 (C,C2), 159.4 (C, C-12), 146.7 (C, C-5), 143.8 (CH, C-4), 139.6 (C, C-7), 137.6 (C, C-9), 132.6 (C, C-8), 115.5 (CH, C-3), 114.4 (C, C-10), 112.9 (C, C-6), 103.3 (CH, C-11), 64.2 (CH_3, C-13), 63.9 (CH_3, C-14), 62.6 (C, C-2'), 30.9 (CH_3, C-1', C-3') ppm.

*Synthesis of methyl 8-oxo-8H-[1,3]dioxolo[4,5-h]chromene-4-carboxylate (**NGs**)*

A suspension of **NG** (0.944 g, 4 mmol) in 75 ml dry ethyl acetate has added to the conical flask envelope with an aluminum sheet and settled in a salt-ice bath. When the temperature of the suspension falls to 0°C, a precooled solution of CH_2I_2 (0.16 ml, 2 mmol) in dry ethyl acetate (6 ml) has dropwise added. The reaction mixture has stirred for 12 hr at 90°C, concentrated to dryness, treated with H_2O (50 ml), and extracted by $CHCl_3$ (3×25 ml). The collected hydrophobic layer has dried on $CaCl_2$, vaporized under vacuum, and the product has recrystallized from CH_2Cl_2 (Mustafa, 2018).

NGs: White powder; m.p.=177-179°C; λ_{max} (EtOH)=279 nm; R_f =0.68; % yield=48.02 (0.476g); FTIR (ν, stretching, cm^{-1}): 3061 (=C-H), 2904 (C-H, alkyl), 1726, 1703 (C=O, ester), 1670 (C=C), 1588 (C=C, aromatic), 1249, 1034 (C-O-C, aryl-alkyl ether); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ= 7.76 (1H, d, J= 9 Hz, H-4), δ 7.53 ppm (1H, s, H-5), δ 6.22 ppm (1H, d, *J*= 9 Hz, H-3), 5.95 (2H, s, H-13), 4.20 (3H, s, H-12) ppm; ^{13}C-NMR (DMSO-d_6, 75 MHz): δ= 170.2 (C, C-11), 160.9 (C, C-2), 155.2 (C, C-7), 145.4 (C, C-9), 143.7 (CH, C-4), 137.5 (C, C-8), 123.3 (CH, C-5), 115.4 (CH, C-3), 113.1 (C, C-10), 110.1 ppm (C, C-6), 93.5 (CH_3, C-13), 53.5 (CH_3, C-12) ppm.

Biological Evaluation

1. Antioxidant Potential

The potential of natural coumarins (**NR**, **NG**) and their matching semisynthetic derivatives (**NRs**, **NGs**) to trap the free radicals of hydroxyl and DPPH has quantified in correlation to ascorbic acid (**AA**) as a standard antioxidant. For each tested derivative, six concentrations (200, 100, 50, 25, 12.5, 6.25 µM) have contrived from a reference methanolic (1mM) solution in the double-dilution manner. With each assay, the % of trapping potential of the derivative expressed as TP% has measured by applying the following mathematic rule: TP% = (A_a – A_d/ A_a) × 100. The A_a and A_d represent the absorbances of **AA** and derivative, respectively. From a diagram that exhibited the correlation between the log concentration of the investigated derivative and TP%, the TP_{50} has calculated for three independent tryouts employing a non-linear regression (Aldewachi et al., 2020).

To test the potential of the derivative for trapping the DPPH radicals, the methanolic solutions of the sample (1.5 ml) and DPPH (0.5 ml, 0.1 mM) have combined. The mixture has laminated with an aluminum sheet to preserve from light, and brooded for 30 min at 25°C. subsequently, the TP% has followed spectrophotometrically at 517 nm utilizing the standard composed of DPPH (0.5 ml, 0.1 mM) and absolute methanol (1.5 ml) (Oglah et al., 2020a).

In the hydroxyl radicals trapping assay, the investigated solution has prepared by mixing the incoming solutions sequentially: the sample (1.5 ml), potassium phosphate buffer pH 7.8 (2.4 ml, 200 mM), $FeCl_3$ (60 µl, 1 mM), o-phenanthroline monohydrate (90 µl, 1 mM), and hydrogen peroxide (150 µl, 170 mM). Next to the incubational period of 5 min at 25°C, the investigated mixture has examined spectrophotometrically at 560 nm

against the standard composed of the mixed solutions but sample (Oglah et al., 2020a).

Primary Antiproliferative Potential

The cells of the selected tumor line have sowed at a density of 4×10^4 per hole in a 96-holes sheet. The holes, incorporated with a compatible medium to the applied cell line, have treated individually in the next 24 hr with mounting concentrations (6.25-200 µM) of the investigated derivatives. The antiproliferative potential of these derivatives has assessed after 72 hr utilizing the tetrazolium dye, MTT. Cell viability assay has conducted by withdrawing the medium, applying the tetrazolium dye (28 µl, 3.27 mM), and then brooding the treated cells for 1.5 hr at 37°C. The antiproliferative percent symbolized as A_p% of each derivative has calculated via the incoming formula: $A_p\% = (H_u - H_t)/H_u \times 100$. The H_u and H_t represent the absorbances of the untreated and treated holes, respectively. The IC_{50} values of the investigated derivatives have determined for three separate experiments by plotting the A_p% versus log concentration and calculated by a non-linear regression (Kubrak et al., 2019).

Antimicrobial Potential

In an antibacterial assay, the selected strain has incubated at 37°C in 5 ml nutrient broth for 16 hr. The final inoculum of 1.5×10^8 CFU/ml has acquired by adjusting the turbidity of the incubated mixture to 0.5 McFarland standard utilizing a normal saline. Discs (0.2 cm in diameter) prepared from Whatman Grade 3 filter papers have moistened with the DSMO solution (10 µl, 20 mg/ml) of the investigated derivative. The incubated mixture (100µl) and molten agar (20 ml) have combined under aseptic conditions and flowed into cell-culture plates. The prepared discs have seeded on the surface of solidified agar by using an aseptic forceps. Upon incubation for one day at 37°C, the inhibition sector (I) of the individual derivative has detected in millimeters via Mitutoyo digital vernier caliper series 500. The activity index (A_I) of the investigated derivative was calculated by applying the incoming mathematical law: $\mathbf{A_I = I_D / I_R}$ (Liya and Siddique, 2018). The symbols $\mathbf{I_D}$ and $\mathbf{I_R}$ represent the inhibition sectors achieved by the investigated derivative and reference, respectively.

In the antifungal assay, a similar technique to that employed for analyzing the antibacterial potential has followed but involving two moderations. These include the incubation for two days at 30°C, and the use of Potato dextrose agar as a culturing medium (Tocci et al., 2018).

Results and Discussion

Chemical Modification

The isolation and structural characterization of the natural coumarins (**NR**, **NG**) have been previously described (Khalil and Mustafa, 2020; Mohammed and Mustafa, 2020). To evaluate the impact of Phenolic hydroxyl groups involving in the chemical structures of these coumarins, two semisynthetic coumarins (**NRs**, **NGs**) have synthesized in such a way to eliminate the role of these functional groups as a hydrogen-bond donor. This structural modification may consequently influence the physicochemical properties, including the hydro- and lipo-philicities (Stefanachi et al., 2011).

For **NR**, the nucleophilicity of its phenolic hydroxyl group has improved via the deprotonation achieved by potassium carbonate. The resulted phenoxide attacks the alkylating agent, DMS, affording the formation of the semisynthetic derivative **NRs**. As a result, the influence of the phenolic hydroxyl group has covered by etherification (Mustafa et al., 2018). Concerning **NG**, the impact of its catecholic hydroxyl groups has shielded by their incorporating into 1,3-dioxolane ring under the effect of CH_2I_2 (Mustafa, 2018).

Biological Evaluation

1. Scavenger effect

The trapping capacity of the natural and semisynthetic derivatives has detected versus the DPPH and hydroxyl radicals. Many research papers reported the effects of various substituents on the antiradical efficiency of many natural and synthetic coumarins. This efficiency has been correlated to the number of phenolic hydroxyl groups linked to the aromatic component of the coumarin backbone (Pérez-Cruz et al., 2018) and to the capability of the substitute ortho to the hydroxyl group to grant electrons (ActaŠeršeň and Lácová, 2015). This correlation is matched with the outcomes reported in Table 1 and Figure 1. In comparison with natural coumarins, the antiradical activity of their parallel semisynthetic coumarins is significantly declined. This may indicate the important role of phenolic hydroxyl group (s) in the antiradical activity of the natural coumarins.

Table 1. The outcomes acquired from testing the scavenger activity of natural and semisynthetic coumarins

Derivative symbol	Scavenger activity versus DPPH free radicals TP_{50} (μM) ± SD (*n*=3)	Scavenger activity versus hydroxyl free radicals TP_{50} (μM) ± SD (*n*=3)
AA	46.29 ± 0.67	50.33 ± 0.91
NR	64.18 ± 0.90	68.48 ± 0.95
NG	48.20 ± 0.86	52.84 ± 0.76
NRs	89.31 ± 1.05	101.06 ± 0.90
NGs	114.05 ± 0.81	107.14 ± 0.72

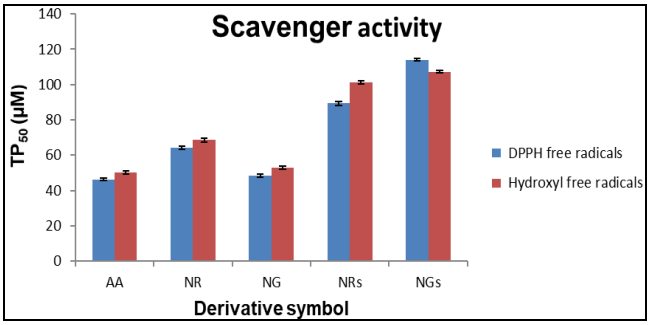


Figure 1. Graphical representation of the outcomes acquired from studying the scavenger activity of the investigated derivatives and positive control.

Primary Antiproliferative Effect

The investigated derivatives have screened for their primary antiproliferative activity utilizing MTT dye, and six different concentrations. This investigation has also incorporated 5-fluorouracil (5-FU) as a standard antiproliferative drug, and DMSO as a solvent. The cancer cell lines involved in this preliminary test include HeLa (Epitheloid cervix carcinoma, 93021013), SK-OV-3 (Caucasian ovary adenocarcinoma, 91091004), AR42J (Rat exocrine pancreatic tumor, 93100618), MCF-7 (Caucasian breast adenocarcinoma, 86012803), AB12 (Mouse malignant mesothelioma,10092306), KYSE-30 (Human Asian esophageal squamous cell carcinoma, 94072011), LC540 (Rat Fischer Leydig cell testicular tumor, 89031604), and AMN3(murine mammary adenocarcinoma).

The outcomes manifested in Table 2 and Figure 2 reported three concerning imports. Firstly, the investigated derivatives have higher IC50 values in comparison with that of 5-fluorouracil. Secondly, the antiproliferative activity of the natural derivatives versus the test cell lines is superior to that of their matching semisynthetic products. Finally, the decline observed in the antiproliferative activity of the semisynthetic derivatives is parallel to the lowering in their antioxidant activity. In the literature, many studies have assigned the antitumor activity of diverse natural and synthetic coumarins with their antioxidant activity (Grigalius and Petrikaite, 2017; Haq et al., 2019; Mendonca et al., 2019).

Table 2. The data collected from testing the primary antiproliferative activity of the investigated derivatives.

Cancer cell line	Derivative symbol				
	5-FU	**NR**	**NG**	**NRs**	**NGs**
HeLa	13.11 ± 0.80	20.18 ± 1.00	25.11 ± 0.90	57.63 ± 1.10	55.54 ± 1.05
SK-OV-3	22.16 ± 1.05	29.58 ± 0.90	31.58 ± 1.00	62.91 ± 0.95	73.36 ± 0.95
AR42J	19.86 ± 0.95	28.09 ± 1.10	30.32 ± 1.15	44.67 ± 0.80	62.48 ± 0.95
MCF-7	12.46 ± 1.10	22.81 ± 1.10	24.17 ± 0.85	47.82 ± 1.20	54.56 ± 0.90
AB12	18.93 ± 1.25	28.90 ± 1.35	28.69 ± 0.80	61.94 ± 1.05	59.18 ± 1.00
KYSE-30	29.38 ± 1.05	40.12 ± 1.05	33.88 ± 0.95	60.87 ± 1.45	67.55 ± 1.15
LC540	23.67 ± 0.85	52.47 ± 1.10	47.17 ± 1.05	83.04 ± 1.20	76.48 ± 1.05
AMN3	24.64 ± 1.20	37.63 ± 1.10	42.11 ± 1.15	49.37 ± 1.00	59.32 ± 1.05

The outcomes have represented as IC_{50} ± SD. The IC_{50} value has computed in μM, while the standard deviation (SD) has enumerated for three separate experiments.

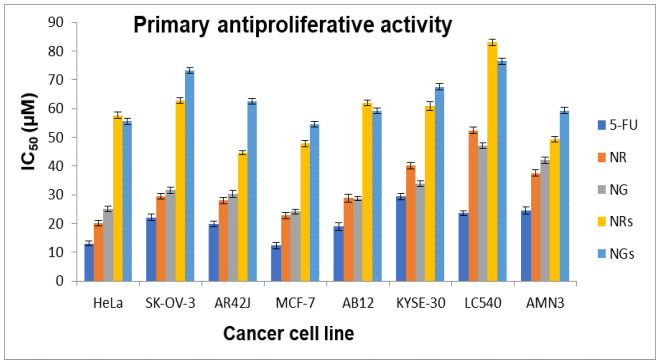


Figure 2. Graphical representation of the data collected from assaying the antiproliferative activity of the investigated derivatives and positive control.

Antimicrobial Effect

The natural and semisynthetic derivatives have scanned for their antimicrobial activity utilizing a well-defined agar disc dissemination method (Mustafa, 2018). This method involved the employment of DMSO as a negative control and a

standard antimicrobial agent as a positive control, which was either ciprofloxacin (10 µg/disc, **CP**) for the antibacterial activity or nystatin (100 units/disc, **NY**) for the antifungal activity.

The test pathogens involved six standard bacterial and three standard fungal sorts. The experimental bacteria include *Escherichia coli* (ATCC 25922, **Ec**), *Salmonella typhi* (ATCC 6539, **St**), *Klebsiella pneumonia* (ATCC 700603, **Kp**), *Haemophilus influenzae* (ATCC 49247, **Hi**), *Shigella dysenteriae* (ATCC 13313, **Sd**) and *Pseudomonas aeruginosa* (ATCC 27853, **Pa**). The fungal sorts encompassed *Candida albicans* (ATCC 10231, **Ca**), *Aspergillus flavus* (ATCC 9643, **Af**), and *Aspergillus niger* (ATCC 16888, **An**).

The data recorded in Tables 3-6 and their graphical representation displayed in Figures 3-6 revealed four considering issues. The first one is the antimicrobial activity of the investigated derivatives is lower than that of the standard. The second issue is the semisynthetic derivatives showed a towering antimicrobial effect in comparison with their corresponding natural products. The third one is the semisynthetic derivative **NRs** has a more inhibitory effect on the growth of the tested bacteria than those of the **NGs** and natural derivatives. The last issue is the semisynthetic derivative **NGs** has a more inhibitory effect on the growth of the tested fungi than those of the **NRs** and the natural derivatives.

Table 3. The outcome assumed from examining the antibacterial activity of the natural and semisynthetic derivatives.

Bacterium	CP	NR	NG	NRs	NGs
Ec	32.63 ± 0.90	10.54 ± 1.15	12.98 ± 1.05	22.16 ± 1.30	19.16 ± 1.25
St	26.12 ± 1.05	9.84 ± 0.95	10.02 ± 1.15	19.50 ± 1.00	14.05 ± 1.20
Kp	31.47 ± 1.00	12.47 ± 1.05	11.59 ± 0.95	20.81 ± 0.95	20.57 ± 1.00
Hi	27.46 ± 1.25	10.46 ± 1.00	12.11 ± 1.05	20.67 ± 1.00	18.82 ± 1.15
Sd	24.56 ± 1.00	8.22 ± 1.00	13.28 ± 1.35	21.04 ± 1.20	21.24 ± 1.05
Pa	35.32 ± 1.05	6.22 ± 0.95	11.67 ± 1.15	18.24 ± 1.05	23.59 ± 0.95

The outcomes represent the means of the inhibition sectors expressed in mm ± SD, which has detected for three separate experiments.

Table 4. The outcome assumed from examining the antifungal activity of the natural and semisynthetic derivatives.

Fungus	NY	NR	NG	NRs	NGs
Ca	19.08 ± 0.90	7.18 ± 1.15	4.44 ± 1.05	11.45 ± 1.10	14.05 ± 0.85
Af	13.67 ± 1.05	6.89 ± 1.00	5.37 ± 0.85	9.11 ± 1.25	11.36 ± 1.05
An	12.22 ± 0.95	6.93 ± 0.90	4.28 ± 0.85	8.14 ± 1.20	9.22 ± 1.10

The outcomes represent the means of the inhibition sectors expressed in mm ± SD, which has detected for three separate experiments.

Table 5. The values of A_I for the natural and semisynthetic derivatives versus the experimental bacteria.

Bacterium	NR	NG	NRs	NGs
Ec	0.32	0.40	0.70	0.59
St	0.38	0.38	0.75	0.54
Kp	0.40	0.37	0.66	0.65
Hi	0.38	0.44	0.75	0.69
Sd	0.33	0.54	0.86	0.87
Pa	0.18	0.33	0.52	0.67

Table 6. The values of A_I for the natural and semisynthetic derivatives versus the experimental fungi.

Fungus	NR	NG	NRs	NGs
Ca	0.38	0.23	0.60	0.73
Af	0.50	0.39	0.67	0.83
An	0.57	0.35	0.66	0.75

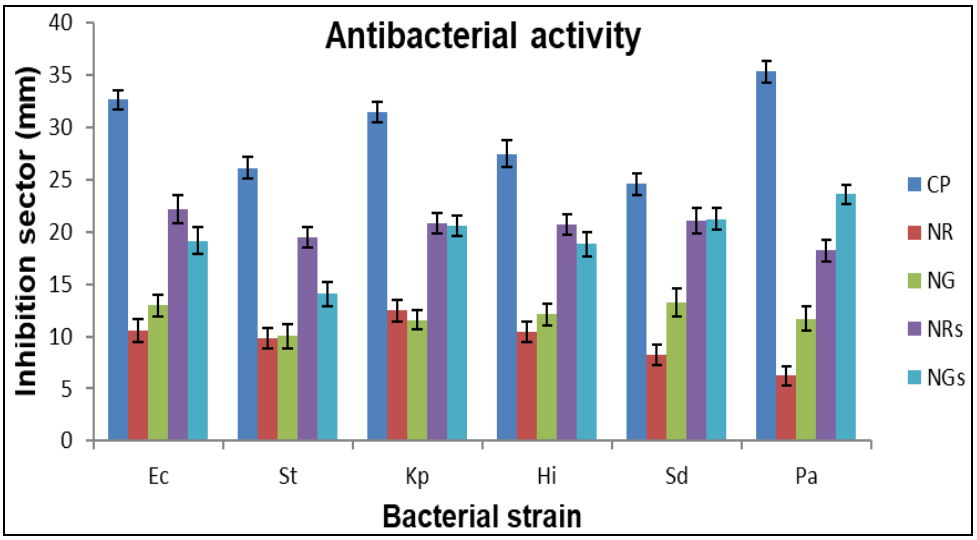


Figure 3. Graphical representation of the data collected from examining the antibacterial activity of the investigated derivatives and positive control.

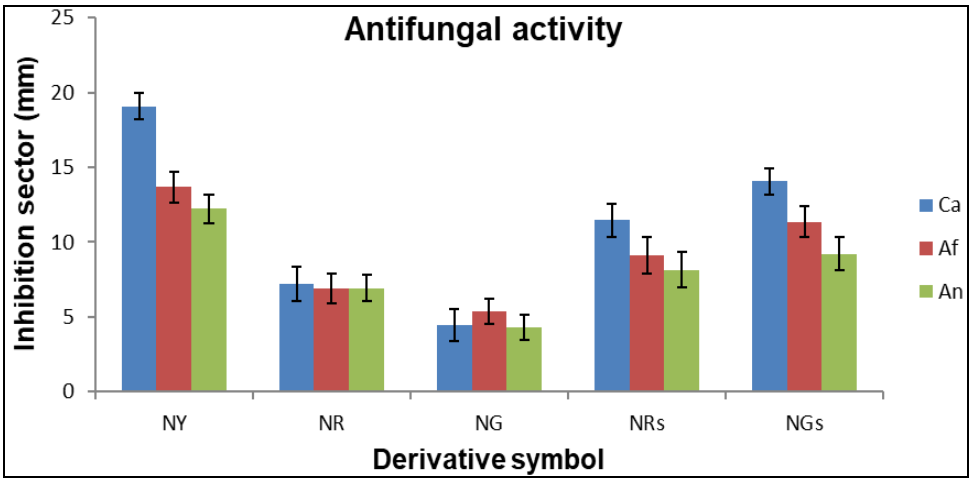


Figure 4. Graphical representation of the data collected from examining the antifungal activity of the investigated derivatives and positive control.

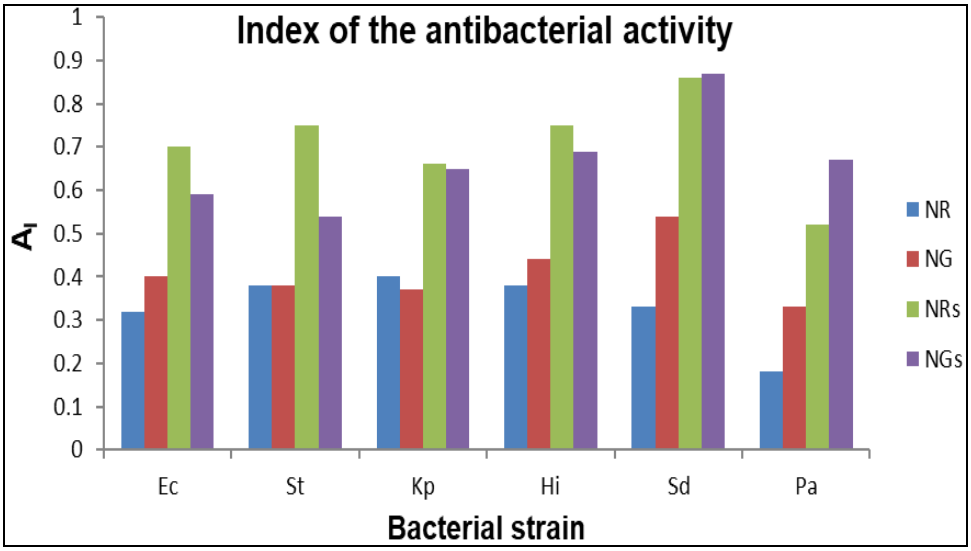


Figure 5. Graphical representation of the A_I values for the investigated derivatives as antibacterial agents.

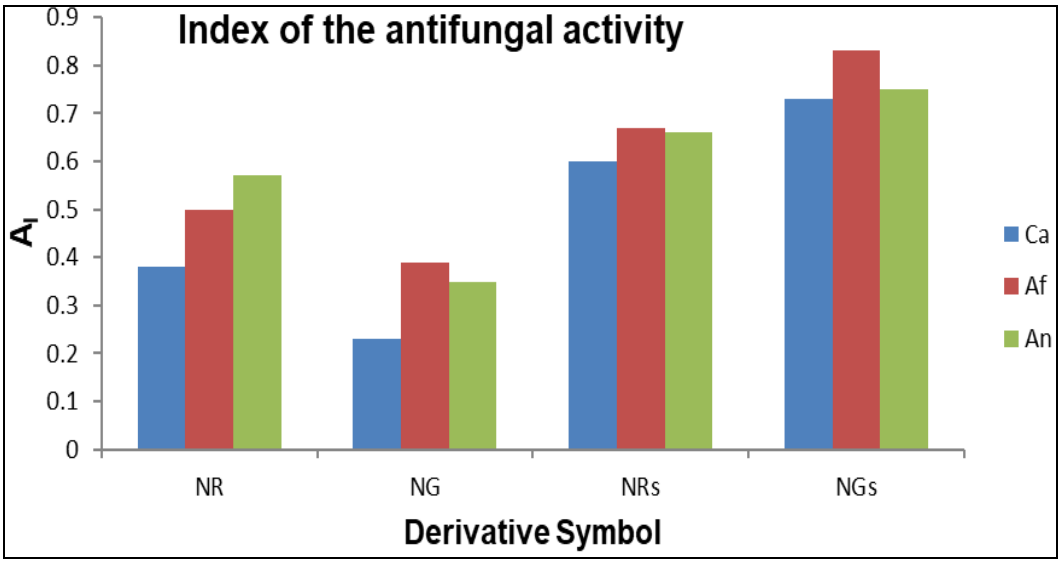


Figure 6. Graphical representation of the A_I values for the investigated derivatives as antifungal agents

The towering antimicrobial activity of the semisynthetic derivatives may assign to the replacement of the hydroxyl group found in their corresponding natural derivatives with less hydrophilic moiety. This replacement may increase the total lipophilicity of the semisynthetic derivatives resulting in the enhancement of their permeation into the infective microorganisms (ONeill et al., 2013; Walasek et al., 2015). Besides, it believed that the presence of two aryl-alkyl ether groups in the ortho or para position to each other could enhance the antimicrobial activity of various nature and semisynthetic coumarins(Khameneh et al., 2019).

Conclusion

This work reported the chemical modification of two natural coumarins to evaluate the role of their hydroxyl group in the biological activity. From the applied studies, it concluded that this modification afforded an improvement in the antimicrobial activity versus the test pathogens. Also, it has dropped the antioxidant and antitumor activities of the natural coumarins in parallel fashion. As a result, the phenolic hydroxyl groups found in the chemical structures of these natural products may play a role in their antioxidant and antitumor activities.

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