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2-(Benzhydryl sulfinyl)-N-sec-butylacetamide) isolated from fig augmented trastuzumab-triggered phagocytic killing of cancer cells through interface with Fcγ receptor

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ABSTRACT

The objective of the current study was to extract 2-(benzhydryl sulfinyl)-N-sec-butylacetamide), a novel compound from fig, and then determine its role in enhancing trastuzumab-triggered phagocytic killing of SKOV-3 cancer cells. In this study, Soxhlet was used to extract the compound from the mature and air-dried fig fruits. The production of the isolated extracts was enhanced by using polar and non-polar solvents. Several solvents, such as methanol, ethyl acetate, chloroform, and n-hexane, were used to isolate the effective compound 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) from the organic layer. UV-spectroscopy, FT-IR, ^{1}H-NMR, and ^{13}C-NMR were applied to identify the purified compound. The *in vitro* and *in vivo* assays demonstrated that the 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) can increase the activity of the phagocytic cells, *via* the interaction with FcY receptors, along with trastuzumab, and the pathway can use a model for the therapeutic strategy for effective treatment of ovarian cancer cells.

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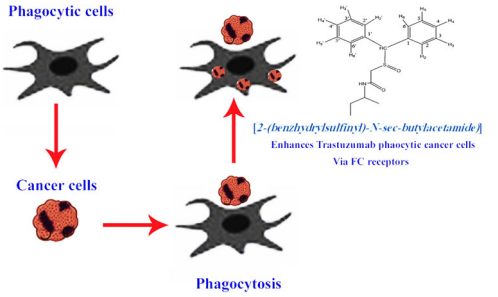

1. Introduction

The immune system comprises a dynamic defensive structure and functions against pathogens, injury, and external and internal injuries (Zhao et al. 2020). The system includes various cells like a macrophage, which takes part in innate and acquired immunity in cancer (Taylor et al. 2005; Al-Omar et al. 2021). The macrophage is an efficient cell to capture pathogens and their antigens, apoptotic, and necrotic (Wynn et al. 2013) because it is provided with several receptors and mechanisms within phagosomes (Zanganeh et al. 2016). It also takes part in the uptake, and presentation of antigens and activation of antigen-specific T cells indicating, its critical role in triggering T cell responses (Mills et al. 2000). While induction of T cell response is necessary for adaptive immunity, the role of the macrophage in inducing phagocytosis is significant. Various drugs have enhanced its phagocytic capacity like trastuzumab (Hu et al. 2020), a humanized mAb used to treat HER2-overexpressing breast cancer (Fiszman and Jasnis 2011). This antibody increases the recruitment of macrophages into the tumor environments inducing the antitumor potentialities; thus, it is an efficient molecule for efficient cancer cell clearance (Kumar et al. 2017).

It is a well-known fact that herbal medicines can work as immunomodulators (Kumar et al. 2012). Among many herbal drugs, figs (*Ficus carica*, Moraceae Family) have been shown to trigger immunomodulation and anti-inflammation (Mawa et al. 2013). Figs, known by more than 135 names, are short deciduous trees grown for their fruits and ornaments (Cheng et al. 2020). They are widely used as an alternative medicine to treat digestive, blood vascular, respiratory diseases, and others, especially by ethnic and indigenous people around the world (Prasad et al. 2006). The fig fruits contain a high level of antioxidant compounds including flavonoids, phenols, and anthocyanin in both the dry and fresh fruits (Solomon et al. 2006). They are also rich in immunomodulatory compounds like *Ficus carica* polysaccharides (FCPS) that have a wide preclinical and clinical significance (Tzianabos 2000; Liu et al. 2009). Besides, they have been evidenced to possess antioxidant, anticancer, cytotoxic, and anti-inflammatory properties. Through *in vitro* and *in vivo* experiments, figs have been shown to be

effective in treating disorders of cardiovascular, endocrine, gastrointestinal, inflammatory, reproductive system, and diseases caused by pathogens (Barolo et al. 2014). Few studies have confirmed the presence of anticancer molecules like bergapten, psoralen, benzaldehyde, amylose, and selenium in fig fruits, and latex (Yang et al. 2017). Thus, it is notable that figs have been interesting for drug and vaccine scientists for many years because of their anticancer properties (Jing et al. 2015). Previously, our research group recorded a number of organic compounds in fig extract that have potential biological activities was detected including 2-benzhydrylsulfinyl-N-sec-butylacetamide (Al-Salman et al. 2020). This compound is less abundant in other fruits and plants. Uniquely, this organic molecule contains both carboxyl group and free sulfur atoms, and due to synergistic effects, it is biologically more active than synthetic compounds (Al-Salman et al. 2020). Therefore, the main objective of this research was to measure the phagocytic activity of bone marrow-derived macrophages (BMDMs) against cancer cells by the 2-benzhydryl sulfinyl)-N-sec-butylacetamide) compound. *In vitro* and *in vivo* tools and techniques show that this compound induces a potent tumoricidal activity against cancer cells *via* the increased trastuzumab action through the interface with FcY receptors.

2. Results and discussion

2.1. UV-spectral diagnosis of extracted compounds

As shown in Figure S1, the direction of the 2-(benzhydryl sulfinyl)-N-sec-butylacetamide was measured at 2.0, 4.0, 6.0, 8.0., and 10.0 μg/ml concentrations. A UV-Vis spectrophotometer at 292 nm was used to determine its absorbance contrasting deionized water (blank), 250 nm aldehyde aromatic, 230 nm meta ring residue, 10 nm para ring residue, 132 nm Ortho NH_2, Total λ_{max} 292 nm (applications: survey scan, test name: 2-(benzhydryl sulfinyl)-N-sec-butylacetamide), start wavelength: 200 nm, stop wavelength: 400 nm). The absorption spectra of an organic compound are influenced by solvent polarity (Figure S2). Interestingly, when the pH increases from 6 to 13 or when the polarity of the solvent is downregulated, the absorption and molar extinction coefficient of tyrosine increases. The linear regression equation obtained from the quercetin standardization was used to determine the quantity of $C_{19}H_{23}NO_2S$.

2.2. FT-IR analysis

FT-IR spectrum (Figure S3), displayed a strong band centered at 1660 cm^{-1} that could be attributed to C = O stretching. In addition, the FT-IR shows a broadly strong band centered at 3206 cm^{-1} could be due to N-H stretching band. The broadening of the N-H band might be because of the underlying hydrogen bonding concept. There were two weak bands at 3032 and 2925 cm^{-1} because of the stretching of aromatic and aliphatic C-H bands, respectively. Furthermore, there were three variable bands between the 698 and 511 cm^{-1} range, and it could be because of aromatic C-H bending. Similarly, the band at 1392 cm^{-1} was attributed to aliphatic C-H bending. Finally, at the range 1510–1400 cm^{-1}, there was a broadly strong band and was due to

asymmetrical stretching of aromatic C = C and S = O bonds. The strong band present at 998 cm^{-1} was associated with the bending of aromatic C = C.

2.3. ^{1}H-NMR spectra analysis

The ^{1}H-NMR spectrum of benzhydryl sulfinylinyl)-N-sec-butylacetamide) was shown in Figure S4. A triplet signal centered at 2.50 ppm was recorded and could be attributed to CH_3CH_2 while a doublet signal centered at 3.12 ppm attributed to CH_3CH. In addition, the signals of CH_2CH_3 and CH_2CO appeared as a doublet centered at 3.60 ppm and a singlet signal at 3.46 ppm, respectively. The heptet signal, which centered at 3.70 ppm due to *CH*-CH_3, while the singlet signal, which appeared at 5.43 ppm, can be assigned to *CH*-Ph proton. On the other hand, the aromatic proton signals of phenyl rings appeared between 7.60–7.25 ppm ($J = 6.0$ Hz). The ^{1}H-NMR spectrum (Figure S4) showed a doublet signal centered at 7.35 ($J = 9.0$ Hz) and 7.33 ppm, respectively, which could be attributed to H2, H2′, H6, and H6′ protons. A triplet signal centered at 7.41 ppm can be attributed to H3, H3′, H5, and H5′ protons ($J = 9.0$ Hz). A doublet signal centered at 7.54 ppm due to H4 and H4′ ($J = 6.0$ Hz). Also, N-H could be assigned at 9.21 ppm because the ^{1}H-NMR spectrum of C appeared as a singlet signal.

2.4. ^{13}C-NMR spectrum analysis

The signals for carbon atoms of 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) can be identified through its ^{13}C-NMR spectrum, which was in good agreement with the suggested structure (Figure 1) and the purity of this compound was 95%. The ^{13}C-NMR spectrum of **C** revealed two signals at 69.00 and 50.20 ppm due to the carbon atoms of **C**H-S = O and **C**H-NH, respectively. Also, two signals appeared at 54.00, and 39.20 ppm can be assigned to methylene carbon atoms of **C**H_2-S = O and **C**H_2-CH, respectively. The signals of methyl carbon atoms of **C**H_3-CH_2 and **C**H_3-CH appeared at 10.10 and 20.75 ppm, respectively. The high chemical shift (low field) signal that was

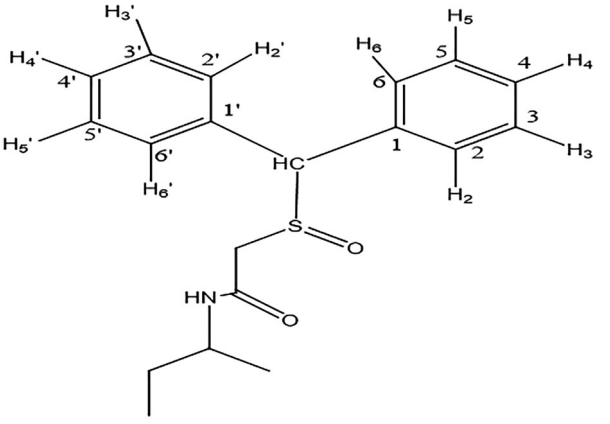

Figure 1. Structure of compound 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) at a purity of 95%.

revealed at 162 ppm can be assigned to the carbon of the ***C = O***. On the other hand, the signals of aromatic carbon atoms of two phenyl rings proved that the two rings were in different magnetic environments. As shown in Figure S5, the ^{13} C-NMR spectrum appeared with the signals of aromatic carbon atoms C2, C2′, C6, and C6′ at 129.50 and 129.8 ppm while the signals at 128.00 and 128.10 ppm due to C4 and C4′, respectively. The signal at 128.60 ppm is assigned to C3, C3′, C5, and C5′. The signals of ipso carbons (*i.e.* C1 and C1′) appeared at 136.00 and 135.6 ppm, respectively. The high chemical shifts of these signals compared with other signals of aromatic carbon atoms due to the resonance effects of phenyl rings made these carbon atoms possess less electron density on them.

2.5. 2-(Benzhydryl sulfinyl)-N-sec-butylacetamide) increases BMDMs phagocytic activity on SKOV-3 cells

The phagocytic nature can be used in the model experiments of phagocytosis of cancer cells and apoptotic cells. In this study, 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) was used to determine whether it could increase the potentialities of BMDMs in killing ovarian cancer SKOV-3. Thus, SKOV-3 cells (phagocytosed cells) were labeled with the fluorescent dye eFluor 670. These cancer cells were incubated with BMDMs as phagocytic cells (2:1, phagocytic: phagocytosed) in the presence of 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) at 25 μg/mL. The CD11b-FITC was used in the BMDMs and cells were analyzed by confocal fluorescence imaging (Figures S6 and S7). The current study aimed to determine the BMDMs population that had both SKOV-3+ and CD11b + cells. Therefore, the percentage of cells positive for both staining was assessed (Figure S8). The results demonstrated an increased CD11b + eFlour 670 + cell population pre-incubated with 2-(benzhydryl sulfinyl)-N-sec-butylacetamide). The data were contrasted with the control group (BMDMs only without fig extracted compound). Data showed that the 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) could enhance the potentialities of trastuzumab in the phagocytosis of ovarian cancer cells.

2.6. 2-(Benzhydryl sulfinyl)-N-sec-butylacetamide) increase the tumoricidal activity of trastuzumab in-vivo

The tumoricidal activity of trastuzumab in the presence of 2-benzhydryl sulfinyl)-N-sec-butylacetamide) was tested using an animal model. Figures S9 and S10 show how the peritoneal macrophages pre-incubated with trastuzumab and 2-(benzhydryl sulfinyl-N-sec-butylacetamide) are revealed. Pretreatment with trastuzumab in the presence of 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) might have enhanced the functional activities of BMDMs against Ehrlich ascites tumor cells. It indicated that 2-benzhydryl sulfinyl)-N-sec-butylacetamide) was potent phagocytosis enhancing compound; thus, it could increase the anticancer potentiality of BMDMs *in vivo*. This molecule might act *via* the release of several molecules like reactive oxygen species (ROS) that could enter into the mitochondria and subsequent activation of macrophages for effective inflammatory and biological consequences.

2.7. 2-(Benzhydryl sulfinyl)-N-sec-butylacetamide) improving phagocytosis activity through Fcγ receptors

We also determined whether 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) enhanced phagocytosis through Fcγ receptors. Fcγ receptors on BMDMs were enhanced following stimulation with IFN-γ. In contrast, these receptors were less increased without stimulation with IFN-γ on BMDMs. Their activities were enhanced following stimulation with IFN-γ by the addition of trastuzumab along with 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) (Figure S11). The results indicated that our model drugs could increase phagocytosis by increasing their Fcγ receptor expression for the effective killing of cancer cells. With the increase of cancer cases, their use has increased from 13% to 63% of cancer patients (Sparreboom et al. 2004). The herbal products possess various compounds like phytosterols, saponins, flavonoids, triterpenes, and carotenoids that are cancer-protective. These phytochemicals are antioxidants and electrophile hunters; thus, they activate the defensive mechanisms, downregulate the generation of carcinogens in nucleotide adducts, and trigger phase I or II detoxification enzymes (Salminen et al. 2008).

The essential role of herbal drugs in tumor chemotherapy has been evidenced by their positive results in the suppression of tumor growth and the improvement of multidrug resistance *in vitro* and *in vivo* (Sun et al. 2009). Commercial drugs contain about 122 chemicals as therapeutic substances derived from plants. In these contexts, chemicals derived from plants have been shown to enhance the phagocytic potentialities of macrophages and subsequently the production of antibodies by B cells (Ranjith et al. 2008). Interestingly, from fig extracts, we have found average and bulky 18 aromatics and nonaromatic with molecules. In these experiments, most chemicals were polar; thus, the solvent polarity and pH were the underlying causes of the absorption spectrum of the organic compound. The chemicals extracted from the cold method differed from those from the warm method. It is associated with the structural transformation of some organic molecules isolated from the hot aquatic layer at high temperatures. A previous study by Coxon and his co-workers demonstrated that the *A. muricata* and *O. aristatus* extracts had immunostimulation for phagocytic cell activity (Coxon et al. 2001). This activity could be due to the presence of active compounds of these plants which stimulate and generate complement factors such as C3b and C3bi which will bind to *E. coli*. Then, this bounded *E. coli* will be recognized by phagocyte receptors such as CR1 (CD35) and CR3 (CD11b). Likewise, the possible mechanism of some plant extract components is rising the overexpression of Fcγ receptor on the phagocyte cells and then encouraging the binding of opsonized *E. coli* to the receptor. The expression of Fcγ receptors such as FcγRIII (CD16) and FcγRII (CD32) will augment the phagocytic activity of phagocytic cells (Butcher et al. 2001).

Importantly, 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) was one of the bioactive chemicals, which was less present in other plants and fruits compared to that in figs. This compound contains both a carboxyl group and free sulfur atoms; it is biologically more potent than synthetic compounds because of their synergistic consequences compounds. We propose that the higher concentration of sulfur combinations is the underlying cause of the therapeutic effects of this compound. The compound's electronic coupling occurs with the plasmalemma and results in the injury, demolition,

and removal of the cell. This compound also possesses four strong bonds C = C, S = O, C = O, and N-H that are due to stretching bonds. We showed here that this compound is polar and present in the aqueous extract.

3. Conclusions

In the current study, the compound is chemically known as 2-(benzhydryl sulfinyl)-N-sec-butylacetamide) and isolated from fig. Using *in vitro* and *in vivo* tools and techniques, we have shown that this compound induces a potent tumoricidal activity against cancer cells *via* the increased trastuzumab action through the interface with FcY receptors. In conclusion, the potent role of the compound in inducing phagocytosis clearly indicates that fig could be used for experimental models and therapeutic strategies for cancer in the future.

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Disclosure statement

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Data availability statement

All the data were provided in the manuscript.

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