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Euro Physical Chemistry 2020-Nature-Inspired Chemical Reaction Optimisation Algorithms-Bina S Siddiqui- University of Karachi

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Abstract:

Recent efforts to develop cure for chronic diabetic complications have led to the discovery of potent inhi-bitors against aldose reductase (AKR1B1, EC 1.1.1.21) whose role in diabetes is well-evident. In the pre-sent work, two new natural products were isolated from the ariel part of Ocimum basilicum; 7-(3-hydroxypropyl)-3-methyl-8-b-O-D-glucoside-2H-chromen-2-one and E-4-(60-hydroxyhex-30-en-1-yl)phenyl propionate (2) and confirmed their structures with different spectroscopic techniques includingNMR spectroscopy etc. The isolated compounds (1,2) were evaluated for in vitro inhibitory activityagainst aldose reductase (AKR1B1) and aldehyde reductase (AKR1A1). The natural product (1) showedbetter inhibitory activity for AKR1B1 with IC50value of 2.095 ± 0.77 mM compare to standard sorbinil(IC50= 3.14 ± 0.02 mM). Moreover, the compound also showed multifolds higher activity(IC50= 0.783 ± 0.07 mM) against AKR1A1 as compared to standard valproic acid (IC50= 57.4 ± 0.89 mM).However, the natural product showed slightly lower activity for AKR1B1 (IC50= 4.324 ± 1.25 mM).Moreover, the molecular docking studies of the potent inhibitors were also performed to identify theputative binding modes within the active site of aldose/aldehyde reductases.

Ocimum basilicum, commonly called as basil, member of theLamiaceae family, which is cultivated commercially in severalregions around the world . More than 150 species of the genusOcimum are known, among them basil is the major crop cultivatedin many countries of the world. From ancient time until now, basilhas been utilized as a popular culinary and medicinal herb. Theleaves and flowers have been extensively used for the treatmentof coughs, headaches, diarrhoea, kidney malfunctions as well asfor its galactagogue, carminative, antispasmodic and stomachicproperties [1–3]. Traditionally, basil has been extensively utilizedin food as a flavouring agent, in perfume and medical industries. Due to its diuretic and stimulating properties, basil have appli-cations in pharmacy . An infusion of basil is considered to bediaphoretic, anti-helminthic, anti-diarrheic and anti-emetic .The juice of basil shows stimulant, carminative actions. While it's essential oil also possesses anti-fungal, anti-bacterial, and insecti-cidal effects . The flowers of this plant are also diuretic, stim-ulant and demulcent in action . The flowers of basil are alsoconsidered to be anti-spasmodic, carminative and digestive stimu-lant . Basil essential oils mainly contain the group of terpenoidcomponents, which includes sesquiterpenes, monoterpenes andtheir oxygenated derivatives . The essential oil mainly exhi-bits anti-fungal and anti-insecticidal activity . Variousresearchers have reported that both Ocimum essential oil and itsvarious extracts were exhibiting antibacterial activities againstgram positive and gram negative bacteria .Ocimum basili-cum is a rich source of bioactive chemicals. Because many of themare largely free from adverse effects and have excellent pharmaco-logical actions, they could lead to the development of new classesof possibly safer anti-diabetic agents and anti-diabetic complica-tion. Additionally, some coumarins and polyphenols and theirsugar derivatives are found to be effective on the inhibitory aldosereductase

Diabetes mellitus (DM) is an incessant disease worldwide.Nearly half a billion world population is affected by DM, ratherabout 80% affected masses belong to developing and under devel oped countries. The close biological and epidemiological proximityof DM and cancer suggest that DM also enhances the possibility ofonset and proliferation of various cancer types . Diabeticcomplications associated with hyperglycemia are majorly com-prised of diabetic retinopathy, cancer, neuropathy, mood disorders,nephropathy and others . Hyperglycemia leads to non-insulin dependent uptake of glucose and triggers the polyol path-way . The polyol pathway is primarily involved in the NADPHdependent reduction of glucose to sorbitol via aldose reductase(AKR1B1) . The metabolic conversion of sorbitol by sorbitol-dehydrogenase enzyme and the reduced penetration of sorbitolincrease the flux of glucose. This increased flux result in highosmotic stress and hence the associated secondary complicationsarise .The aldehyde reductase (AKR1A1) and aldose reductase(AKR1B1) belong to aldo-ketoreductase (AKR) superfamily catalyz-ing the reduction of corresponding aldehydes and ketonesinvolved. Both the closely related enzymes AKR1A1 and AKR1B1have 65% structural similarity and differ only at the active site.While AKR1B1 is mainly involved in polyol pathway, AKR1A1 isresponsible for reductive detoxification of reactive aldehydes,and metabolizes methyl glyoxal and 3-deoxyglucosone which haverole in the formation of toxic glycation end products . Alde-hye reductase (AKR1A1) being a member of AKR superfamily hassignificant role in various biological processes such as regulationof proinflammatory response through the reduction of aldehydephospholipids . Since many aldose reductase inhibitors (ARIs)has been reported, but none of them get success in advance clinicaltrial, and so far only one make been marketed; Epalrestat, ONOPharmaceutical, Osaka, Japan . Use of isolated natural productswould be potentially beneficial to find good lead as ARIs Evidenceshowed that the inhibition of polyol pathway is an attractive chal-lenge to alleviate the diabetic complications

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and aldose reductaseinhibitors (ARIs) can play significant role in that. A large numberof ARIs mainly hydantoin and carboxylic acid derivatives haveentered into clinical trials, the only marketed drug is Epalrestatwhich is rhodanine based . During clinical trials the unfa-vourable profile of AKR is attributed to their non-selectivity and adverse side effects. AKR1A1 selective towards AKR1B1 with safepharmacophore are highly desirable to suppress polyol pathwayand hence reduce chronic diabetic complications.In our current study, we designed to isolate some new naturalproducts from the above mentioned plant (basil) and characterizedthem with different spectral techniques such as1H,13C NMR and2D NMR spectra, IR and mass spectrometry. The natural product contains coumarin and glucose scaffolds while compounds (2)structure is simply a functionalized benzene ring. A range of cou-marin based compound of plant original has been reported asAKR1B1 inhibitors . In our recent study, we have reported cou-marin compounds as aldose reductase (AKR1B1) inhibitors .The structure an active molecule . The isolated compounds were evaluated as anti-diabeticagent via inhibition assay of aldose reductase.

Conclusion:

Two new natural products 7-(3-hydroxypropyl)-3-methyl-8-b-O-d-glucoside-2H-chromen-2-one and E-4-(60-hydroxyhex-30-en-1-yl)phenyl propionate has been isolatedfrom Ocimum basilicum. The isolated compounds were evaluatedfor their inhibitory activity against aldose reductase (AKR1B1)and aldehyde reductase (AKR1A1). The compound 1containingcoumarin and glucose scaffold was found to more potent againstAKR1B1, an key enzyme of polyol pathway which flux glucose,with IC50value of 2.095 ± 0.77 mM compare to standard sorbinil(IC50= 3.14 ± 0.02 mM). The natural product 2, although a simplefunctionalized benzene ring based molecule, yet showed activity(IC50= 4.324 ± 1.25 mM) slightly less than standard sorbinil andcan be modulate via simple chemical modifications. Altogether,the current study provides two molecules which could potentialserve as lead for the development of AKR1B1 inhibitor for the cureof diabetic complications.

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