Antiinflammatory drugs inhibit both COX 1 and COX 2 inhibition causes side effects (related to gastrointestinal and cardiovascular) 43,46 and COX-2 inhibition is responsible for therapeutic effects 45. NSAIDs are particularly used for reducing pain and inflammation 16 in osteoarthritis, rheumatoid arthritis, and arthritis of systemic lupus erythematosus, psoriasis and other seronegative spondyloarthropathies. These agents block metabolism of arachidonic acid through the enzyme cyclooxygenase, and therefore, the production of prostaglandins 45. NSAIDs are associated with side effects such as: formation of gastric ulcers, including lesions of the gastric, duodenal, intestinal mucosa and dyspepsia 47,48, due to the presence of free carboxylic acid. The chronic use of NSAIDs for a long time induces ulcer in the range of 15-30% 49. Some marketed drugs such as; sulindac and fenbufen cause minimal risk of acute injury to the stomach. 1,3,4-Oxadiazoles have been designed for reducing the gastric ulcer formation because of their enzyme inhibiting properties for both cyclooxygenase and 5-lipoxygenase 33,51. Some novel compounds have designed by replacement of the carboxylic acid group with 1,3,4-oxadiazole nucleus have resulted in a significant antiinflammatory activity. In oxadiazoles, substitution at C-2 and C-5 positions with acetoxophenyl, dimethoxyphenyl, methoxyphenyl, chlorophenyl has resulted in significant improvement in the antiinflammatory activity 52,53. The most common method used for the synthesis of 1,3,4-oxadiazole nucleus involves the cyclization of hydrazides with a variety of anhydrous reagents, such as thionyl chloride, phosphorus oxychloride, boron trifluoride etherate, 1,1,1,3,3,3-hexamethyldisilazane 28, phosphorous pentoxide, triphenylphosphine and triflic anhydride giving good yield under harsh or neutral reaction conditions 22,38,40. Antiinflammatory activity of the synthesized compounds evaluated by carrageenan induced rat paw oedema method 37,53.
synthesized compounds, they found that, compounds 1 and 2 showed better antiinflammatory activity against the standard (indomethacin). Antiinflammatory activity of 1,3,4-oxadiazole derivatives was enhanced by the direct substitution at C-2 position with pyridinyl and benzoic acid, and also at C-5 position with pyridine.

G Nagalakshmi synthesized novel derivatives of 1,3,4-oxadiazole, and tested them for their antiinflammatory activity, using carrageenan-induced rat paw oedema method. They prepared 2,5-disubstituted-1,3,4-oxadiazoles, by the condensation reactions of 4-methoxybenzohydrazide, with different aromatic acids in the presence of phosphoryl chloride. It was found that compound 3 N-[4-{5-[4-(methoxy-phenyl)-1,3,4-oxadiazol-2-yl]-phenyl}benzamide exhibited potent antiinflammatory activity with 50 %, as compared to the standard drug phenylbutazone, with 53.57 %.

Asif Husain et al synthesized 2-[3-[4-chlorophenyl]propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole and 2-[3-(4-ethylphenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole 3-[4-chlorobenzoyle] propionic acid derivatives. They screened them for their good antiinflammatory activity using carrageenan induced rat paw oedema method. They found that compounds 2-[3-[4-chlorophenyl]propan-3-one]-5-[4-methoxyphenyl]-1,3,4-oxadiazole 4a and 2-[3-[4-chlorophenyl]propan-3-one]-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole 4b showed significant antiinflammatory activity, with 58.38 % and 59.52 %, respectively, when compared to the activity of indomethacin, with 64.28 % inhibition. They indicated that the presence of 4-methoxyphenyl or 3,4-dimethoxyphenyl substitution at C-5 position of oxadiazole ring causes remarkable improvement in antiinflammatory activity.

Asif Husain et al synthesized a novel series of 1-[4-phenoxyphenyl]-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-one by condensation reaction of diphenyl ether with succinic anhydride, in the presence of anhydrous aluminium chloride, followed by the Friedel-Crafts acylation reaction, via an intermediate compound 3-[4-phenoxybenzoyle] propionic acid, using different aryl acid hydrazides, in the presence of phosphorus oxychloride. Amongst of these compounds, 3-[5-(2-acetoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-[4-phenoxyphenyl] propan-1-one 5a and 3-[5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-[4-phenoxyphenyl] propan-1-one 5b showed excellent antiinflammatory activity, with 65.63 % and 62.50 %, respectively, when compared to the activity of indomethacin with 68.75 %, and greater than that of 3-[4-phenoxybenzoyl] propionic acid (parent compound) with 43.75 %.

Asif Husain et al synthesized a novel series of 2-[3-[4-bromophenyl]propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles 6 by the condensation reaction of bromobenzene with succinic anhydride, in the presence of anhydrous aluminium chloride, following Friedel-Craft’s acylation reaction, via an intermediate compound 3-[4-bromobenzoyl] propionic acid. All of these compounds were evaluated for their in vivo antiinflammatory activity by the carrageenan induced rat paw oedema method, with minimum or without ulcerogenic activity.

Biological evaluation of these compounds showed that compounds 2-[3-[4-bromophenyl]propan-3-one]-5-[4-chlorophenyl]-1,3,4-oxadiazole 6a and 2-[3-[4-bromophenyl]propan-3-one]-5-[3,4-dimethoxy phenyl]-1,3,4-oxadiazole 6b exhibited good antiinflammatory activity, with 59.5 % and 61.9 % respectively, compared to that of indomethacin, with 64.3 % activity.

Harish Rajak et al synthesized a new series of oxadiazoles and evaluated their antiinflammatory activity. Compound 7 was found to be the most active compound of this series due to the presence of 4-hydroxy group on the benzene ring attached to C-2 position of the oxadiazole. They indicated that at doses of 100 mg/kg, the compound exhibited 55.93 %, 36.64 % and 49.33 % protection against carrageenan induced rat paw oedema, moist cotton pellet-induced granuloma and dry cotton pellet-induced granuloma, respectively.

Shashikant V. Bhandari et al synthesized eight compounds, a series of S-substituted phenacyl 1,3,4-
oxadiazoles 8 derived from 2-[(2,6-dichloroanilino)phenyl]acetic acid (diclofenac acid). They indicated their better antiinflammatory activity in the carrageenan induced rat paw oedema model, with no GI toxicities, compared to the standard drug diclofenac sodium. Esterification of 2-[(2,6-dichloroanilino)phenyl]acetic acid (diclofenac acid) followed by treatment with hydrazine hydrate in absolute ethanol, afforded 5-[(2,6-dichloroanilino) benzyl] 2-mercapto-1,3,4-oxadiazole 8\(^\text{55}\).

Asif Husain et al synthesized a new series of oxadiazole derivatives and evaluated them for their potent antiinflammatory activity using carrageenan induced rat paw oedema method. The synthesis of 3-[5-{(substituted aryl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-yl)prop-1-ones 9 by condensation reaction of biphenyl with succinic anhydride, in the presence of anhydrous aluminium chloride, followed by the Friedel-Craft’s acylation reaction conditions, via an intermediate compound 4-oxo-4-(biphenyl-4-yl)butanoic acid. Biological evaluation of these compounds indicated that antiinflammatory activity of compounds 9a and 9b were more selective towards COX-2, as indicated by COX-2 selectivity index of 36.06 and 29.05 (COX-2 IC\(_{50}\)=1.5 \(\mu\)M and 1.8 \(\mu\)M), respectively, due to the presence of 4-methoxyphenyl or 3,4-dimethoxy phenyl substitution at the C-5 position of the oxadiazole ring. They found that compound 9b was the most potent compound of this series, more potent than parent compound fenbufen, when compared to diclofenac\(^\text{56}\).

Pooya Chawla et al synthesized a novel series of [5-(4-chloro-phenyl)-][1,3,4]oxadiazol-2-yl]-pyridine 10 and 2-(4-substituted phenyl)-5-(2-aminophenyl)-1,3,4-oxadiazole 11. The treatment of esters and hydrazine hydrate in the presence of ethanol, via intermediate steps isonicotinic acid hydrazide and 2-aminobenzohydrazide respectively, followed by reaction with phosphorus oxychloride and various aromatic acids, afforded different 1,3,4-oxadiazoles. From all the synthesized compounds, they found that compounds 10 and 11 exhibited significant antiinflammatory activity\(^\text{57}\).

K C Ravindra et al synthesized 2-naphtho[2,1-b]furan-2-yl-1,3,4-oxadiazoles by the condensation reaction of naphtho[2,1-b]furan-2-carboxyhydrazides with different aldehydes, via an intermediate N-[1(E)-arylmethylene]-naphtho[2,1-b]furan-2-carboxyhydrazides. Of all the synthesized compounds, they found that compound 12 exhibited significant antiinflammatory activity\(^\text{58}\).

Mohammad Amir et al synthesized 2-substituted aryl-5-{2,4,6-trichlorophenoxy-methyl]-1,3,4-oxadiazoles 13 by the reaction of 2,4,6-trichlorophenol and ethylchloroacetate, in the presence of potassium carbonate, via an intermediate compound 2,4,6-trichlorophenoxy acetic acid, using different aromatic acids or arylalkanoic acids, in the presence of phosphorus oxychloride. They evaluated them for their biological activity by carrageenan induced rat paw oedema method. These study revealed that 13a and 13b possessed moderate antiinflammatory activity\(^\text{59}\).

Mohammad Amir et al synthesized 5-{(4-hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazoles and evaluated them for their biological activity. The treatment of 4-hydroxyphenylacetic acid with hydrazine hydrate in absolute ethanol gave 4-hydroxyphenyl acetic acid hydrazide. Further treatment with various aryl/alkyl isothiocyanates produce N-{[2-[4-hydroxyphenyl]acyt] N-aryl/alkyl-3-thiosemicarbazides, which were then and cyclized to form oxadiazole 14 in the presence of iodine and potassium iodide. Of all the synthesized compounds, 5-(4-hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazole 14 exhibited significant antiinflammatory activity with 77.77 \%, due to the presence of a 4-methoxyphenylamino group at the second position of the oxadiazole ring\(^\text{60}\).

Mohammad Amir et al synthesized novel derivatives of ibuprofen 1,3,4-oxadiazoles by cyclization of 2-[4(i-butylphenyl) propionic acid hydrazide and N-[2-[4(i-butylphenyl)]-propionyl]-N-alkyl/aryl-thiosemicarbazides. All these compounds evaluated for antiinflammatory activity and less ulcerogenic activity, compared to ibuprofen, through the severity index 0.5 to 0.8, vs. ibuprofen 1.8. They found that compound 15 [5-{1-[4-isobutyl-phenyl]-ethyl]-1,3,4]oxadiazol-2-yl]-propylamine showed significant antiinflammatory activity which
is comparable to standard drug ibuprofen. The significant activity is due to the presence of n-propyl amine.

Priya V Frank et al synthesized a series of 1,3,4-oxadiazole derivatives containing nitroimidazole, moiety and evaluated them for their antiinflammatory activity, using formalin-induced rat paw oedema method. Microwave irradiation of 2-methyl-4-nitro-1-imidazo-acetohydrazide with suitable carboxylic acids, in the presence of phosphorus oxychloride, afforded 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles. They found that 2-(4-methoxy-phenyl)-5-(2-methyl-4-nitro-imidazol-1-ylmethyl)-[1,3,4]oxadiazole 16 was the most potent compound of this series, with good yield.

R. R. Kamble et al synthesized novel 1,3,4-oxadiazole derivatives, and tested them for their antiinflammatory activity. Bromination of P-acetylphenylsydnone, in presence of acetic acid, gave 4-bromo-3-(p-acetylphenyl)sydnione at room temperature. Further treatment with aromatic aldehydes gave 4-bromo-3-[P(3'-aryl-acetyl-1'-oyl)] phenylsydnione, in presence of acetic anhydride. 1,3-Dipolar cycloaddition, by the elimination of bromine, afforded 5-methyl-3-[P(3'-aryl-acetyl-1'-oyl)-phenyl]-3H-Δ2-2-oxo-1,3,4-oxadiazole. By the nucleophilic addition of amino group and intermolecular dehydrative cyclization, they synthesized the final compound 5-methyl-3-[P(6'-aryl-2'-thioxo-1',2',5',6'-tetrahydro[1,3,4]oxadiazol-3H-2-oxo-Δ2-1,3,4-oxadiazole. Compound 17 was to found have an excellent antiinflammatory activity.

Asif Husain et al synthesized novel derivatives of 1,3,4-oxadiazole. The condensation reaction of diphenylmethane and succinic anhydride, in the presence of aluminium chloride, gave β-(4-benzylbenzoylepropionic acid), followed by Friedel-Craft's acylation reaction. On further treatment with aryl acid hydrazides, in the presence of phosphorus oxychloride, 1-(4-benzylphenyl)-3-(5-substituted-1,3,4-oxadiazole-2-yl)-1-propanone was obtained. From biological evaluation of all the synthesized compounds, it was concluded that compound 18 possessed good antiinflammatory activity.

Shivananda Wagle et al synthesized novel 2-(3-methyl-7-substituted-2-oxoquinolin-5-yl)-5-(aryl)-1,3,4-oxadiazole compounds, and evaluated them for their potent antiinflammatory activity. Of all the synthesized compounds, 1-[5-(4-methoxy-phenylsulfonyl)-[1,3,4]oxadiazol-2-ylmethyl]-3,7-dimethyl-1H-quinolin-2-one 19 showed maximum antiinflammatory activity.

F. A. Omar et al synthesized novel substituted 1,3,4-oxadiazole derivatives, and evaluated them for their potent antiinflammatory activity. They found that compound [5-(1,2-dihydro- pyridin-2-yl)-[1,3,4]oxadiazol-2-yl]-phenyl-amine 20 exhibited good antiinflammatory activity.

Sudha et al synthesized 5-(4-aryl)-aryloxy-methyl-2-thiol-1,3,4-oxadiazole derivatives, and evaluated for their antiinflammatory activity. Biological evaluation of the synthesized compounds showed that 5-(4'-chloro-3-methyl-biphenyl-4-yl)oxadiazole-2-thiol 21 was the most potent compound, as compared to other synthesized drugs. These compounds also showed good antibacterial, antifungal and diuretic activity.

Saxena et al synthesized novel series of 1,3,4-oxadiazole derivatives and screened them for their antiinflammatory activity. They found that the compound 5-(3-chlorophenyl)-3H-[1,3,4] oxadiazole-2-thione 22, containing 3-chloro group showed potent antiinflammatory activity.

Jose M. dos Santos Filho et al synthesized novel oxadiazole derivatives containing two oxadiazole rings (1,2,4 and 1,3,4 oxadiazoles). The treatment of 1,2,4-oxadiazole carbohydrazides with phenyl isothiocyanate led to the formation of compound 23, via an intermediate thiosemicarbazide derivative. Compounds 23a and 23b showed good antiinflammatory activity amongst all the synthesized compounds.
CONCLUSION

This review article mainly focused on potent antiinflammatory activity of 1,3,4-oxadiazoles with lesser side-effects, which has global therapeutic and clinical importance. 1,3,4-Oxadiazole derivatives also show various important pharmacological activities and are widely used for preparation of medicinal active compounds. This activity is exploited for awakening the safe use of this important chemical moiety with minimal or no ulcerogenic activity in future. This summarized study would be useful for the researchers working in this field.

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