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A Review: Green Synthesis of Chalcone

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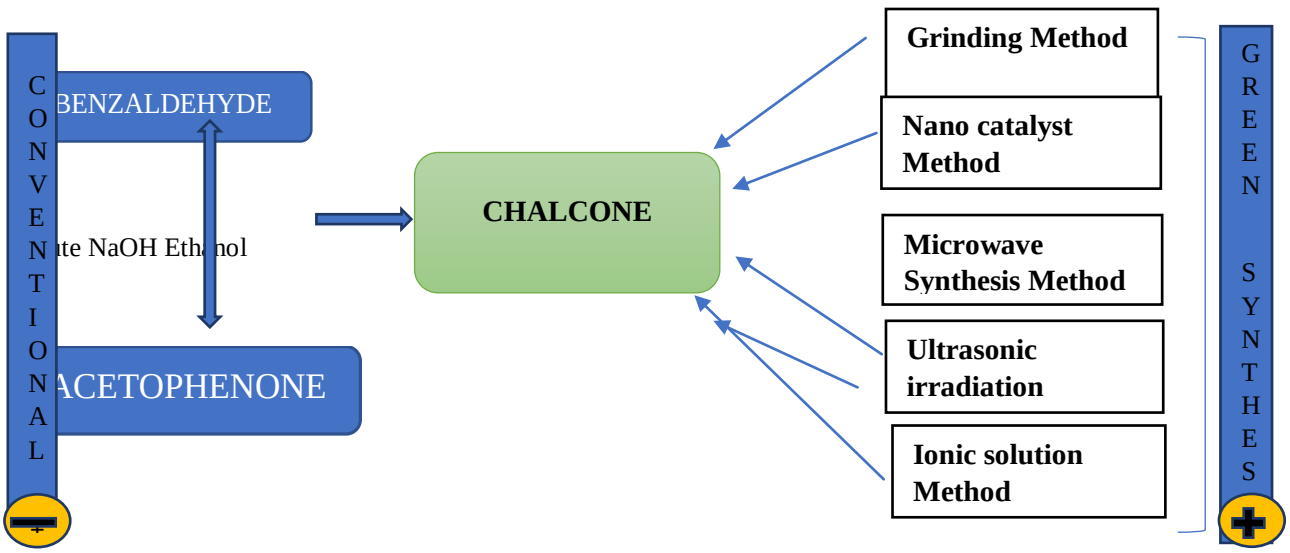
***Abstract*:-**

Chalcone is very promising drug molecule in modern day pharmaceutical field. This molecule has own various types of biological activity like anti-bacterial,anti-inflammatory,anti-amoebic,anticancer etc. If any electron withdrawing group like chloro,bromo, nitro etc. and any heteroaromatic ring insert into chalcone group or any heteroaromatic ring add by replace of any phenyl ring of chalcone then the potency and biological activity of chalcone will be enhanced. This is a review paper about finding suitable method for chalcone synthesis via green chemistry approaches.Recently green chemistry is emerging as a new goal of pharmaceutical industry. In this review, green chemistry methods are compared with conventional methods and ultimately which method is best this will be discussed. Conventionally method for synthesis of chalcone has many drawbacks,which are discussed later,green chemistry methods overcome this problem. In this article we have discussed about the conventional and all green synthetic methods of chalcone. Also discussed the all drawbacks of conventional methods and the advantages of green synthetic method over conventional method and determine the best green synthetic method for preparation of chalcone.

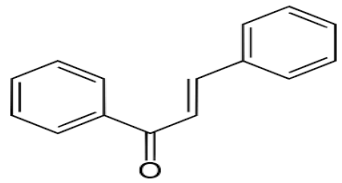
Keywords:*Chalcones, Green synthesis, Sustainable chemistry, Medicinal chemistry, Eco-friendly catalysts*



1. Introduction

Chalcone is a very important drug molecule which is widely used into pharmaceutical field. It's use as antibacterial [1], anti-inflammatory [1] [2], anti-amoebic, anticancer [4], antidiabetic [4], antioxidant [7], antiparasitic[8] etc.It's available in various formulation in the market.Chalcone obtain naturally from Leguminosae plant and rutaceae plant like citruses fruits and vegetables (tomatoes,bean,potatoes) etc.[5,7,8]. The most significant chalcones are flavokawin, butein, 4-hydroxyderricin, cardamonin, dihydroxychalcone etc. It's important intermediate for synthesis of flavone [14,15]. Naturally obtain chalcone is not properly pure and yield value is not satisfactory so synthesis of chalcone is require for preparation of drug molecule.The name of chalcone was first given by Kostanecki,Tambor.[6]

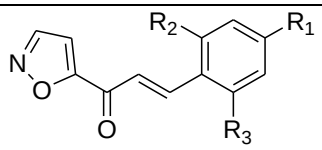
Chemistry and Property:

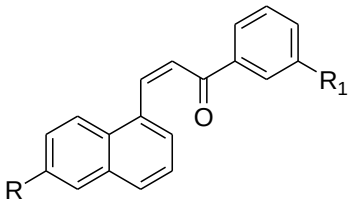
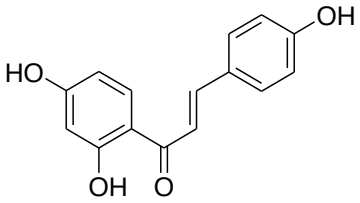
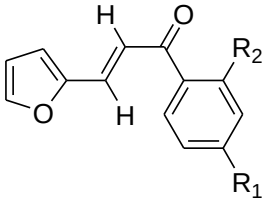
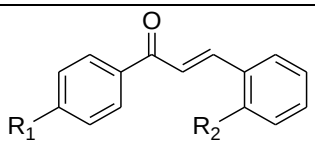
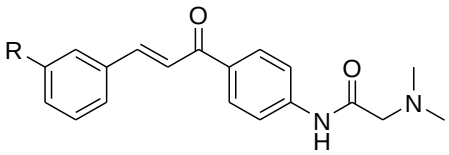
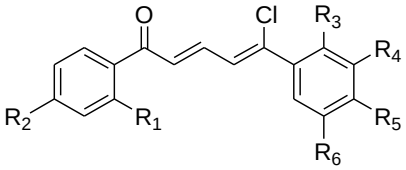


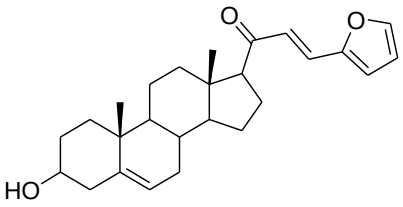
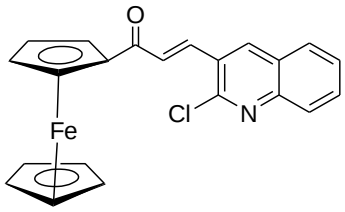
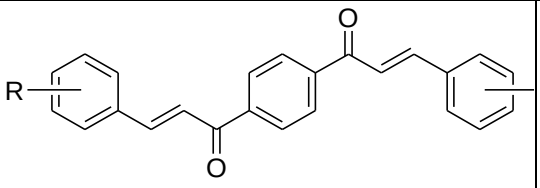
Chalcone
Fig.1

The chemical name of chalcone is benzyl acetophenone or benzylidene acetophenone.Fig.1 depicts chalcone as having two aromatic rings and one, β-unsaturated carbon atom. Chalcone is the progenitor of the flavonoids and isoflavonoids found in abundance in Indonesian flora [7,10]. Chemically, chalcone consists of an open flavonoids chain in which two aromatic rings are connected by an aliphatic three-carbon chain in the, α-unsaturated and β-unsaturated carbonyl system. It is a particular form of alpha, beta unsaturated ketone [3-5]. Chalcone is known by its IUPAC name, 1,3-diphenyl-2-propen-1-one. It is used as a ubiquitous natural pigment and is an essential intermediate in the biosynthesis of flavonoids. Chalcone has the chemical formula C15H12O[2]. The physical propertiesof chalcone such asmolar mass 208.260g/mol, density 1.071g/cm^3,melting point is 55-57 degree celcious, boiling point is 345-348 degree celcious.The appearance of chalcone is pale yellow solid.[5] Chalcone have two absorption maxima at 280 and 340 nm.[9,10]Chalcone soluble in non-polar solvent like benzene,chloroform and insoluble in water.[6]It's harmful if swallowed and irritating to skin,eyes. Chalcones derivatives have various types of biological activity. Into chalcone structure the 'E' structural conformation is more stable than 'z' conformation due to huge steric repulsion between phenyl ring and carbonyl group of 'z' isomer.[2]

The name of various chalcone derivatives and their biological activities are presented at Table 1.

Compound No.	Derivatives name	Structure	Structural modification	Biological activity	References
(2)	Isoxazole chalcone		R_1,R_2,R_3= (-OCH_3)	Antiparasitic	[3]
			R,R_3= (-OCH_3) R_2= -Cl	Antifungal	

(3)	Naphthyl chalcone		R_1= (-OCH_3) R= -Cl	Antitubercular	[4]
(4)	Isoliquiritigenin		-OH group add into chalcone	Anti-inflammatory	[4], [5]
(5)	Furan based chalcone		R_1 = NO_2 R_2 = H	Anticancer	[6]
(6)	Disubstituted chalcone		R_1= -OH R_2= -NO_2	Antioxidant	[1], [2]
(7)	Amine based chalcone		R= EWG (-cl, -Br, -NO_2)	Treat antibiotic resistant pathogen like (*S.aureus, E.coli*)	[1], [2]
(8)	Chlorinated chalcone		R_1=R_2= EWG R_3/R_4/R_5= heteroaromatic ring	Antibacterial (*S.aureus, E.coli*)	[2]

(9)	Steroidal chalcone		Steroid ring attaches with chalcone ring	Antibacterial (*E-coli,B. subtilis*)	[2]
(10).	Ferrocene chalcone		Ferrocene ring attach with chalcone ring	Antibacterial (*T. vaginalis*)	[2]
(11)	Bis-chalcone		R substituted by EWG or heteroaromatic ring	Antibacterial (*E.coli, Candida albicans*)	[1]

Without this chalcone derivatives many other types of chalcone derivatives are also present into pharmaceutical field such as indole based chalcone, fluorinated chalcone,pyrazoline chalcone etc.

Green Chemistry:[5],[10]

Green chemistry is concerned with research that reduces or eliminates environmental impacts. The primary objective of green chemistry is to prevent the production of waste that is detrimental to the environment and to generate substances that are non-toxic to humans and the atmosphere, thereby maximizing atom economy. This is accomplished by ensuring that the final product contains as much of the starting materials as possible and avoiding the use of hazardous solvents.

The numerous principles of green chemistry are as follows: a) Eliminate waste material; b) Atomic economy[11]; c) Reduce hazardous synthesis[12]; d) Design pioneer chemicals; e) Nonhazardous solvents and auxiliaries; f) Design energy efficiency[13]; and g) Use of renewable feedstocks. h) Reduce derivatives i) Catalysis k) Design for degradation[14,15] l) Real-time analysis for pollution prevention m) Chemistry that is inherently harmless for accident prevention

a) Obstruct waste:- Into this type of reaction reduce the amount of waste materials, so environment will be free of chemicals.

b) Atom economy:- Hence which amount of reactant molecules participates into reaction, this equal no of molecules contain products will form. So no loss of any reactant molecule.

c) Less hazardous synthesis:- Into this synthetic reaction which products are form this are less toxic in nature, eco-friendly with nature.

d) Design benign chemicals:- Hence which types of chemicals participate into reaction, they have no toxic effect into environment and not harmful in nature.

e) Benign solvents and Auxiliaries:- Hence which type of polar, non-polar solvent use into reaction they have no toxic effect into environment and not harmful in nature.

f) Design energy efficiency:-Hence which type of reaction will be designed, this reaction should be energy efficiency in nature, not require much more energy for complete the reaction.

g) Use of renewable feedstocks:- Into this reaction which products are formed they are renewable, so it's eco-friendly in nature.

h) Reduce derivatives:- Hence a smallernumber of by-products are formed. So pure products are form.

i) Catalysis:-The rate of reaction is increased by help of catalysis; activation energy will be low so the reaction quickly complete.

k) Design for degradation:- Into this reaction which products are form they are easily biodegradable in nature, not persist into environment for long time.

l) Real time analysis for pollution prevention:- It's not time-consuming process. This type of reaction environment will be less polluted.

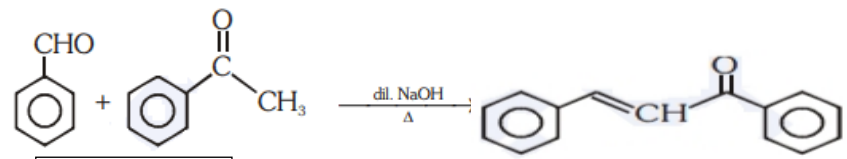
m) Inherently benign chemistry for accident prevention:-Hence which type of reaction is design that no accident not occur during perform of the reaction, so the environment not polluted so much and population not suffer by chemicals.

Hence various types of green synthetic methods are present and comparison between this green chemistry methods and conventional methods for synthesis of chalcones are present. Conventional method for synthesis of chalcone has many drawbacks, green synthetic methods overcome this problems.

Conventional Route for synthesis of chalcone:[5],[10]

In the laboratory, chalcone can be produced via the Claisen-Schmidt reaction by combining aromatic ketone compounds such as acetophenone or their derivatives with aromatic aldehyde compounds such as benzaldehyde or their derivatives in the presence of strong bases used as catalysts such as NaOH, KOH, Ba(OH)2, LiOH.2H2O in polar solvents such as ethanol. In this reaction, other catalysts such as sodium phosphate and aluminum-magnesium hydroxide hydrate can also be used.

Synthetic Route:- At first the required amount of benzaldehyde mixed with acetophenone with continuous stirring. Then added the newly prepared sodium hydroxide solution into this previous solution mixture. At last added ethanol like polar solvent in this solution. Now solution mixture was stirred by mechanical stirrer into RT until the yellowish precipitate was fallen under reaction media. Then refrigerated this solution mixture overnight and then the mixture was filtered.Thus, the crude chalcone was prepared. Then it was recrystalized by hot ethanolic solution.



Benzaldehyde | Acetophenone | Chalcone + H_2O**[10]**

Fig.12

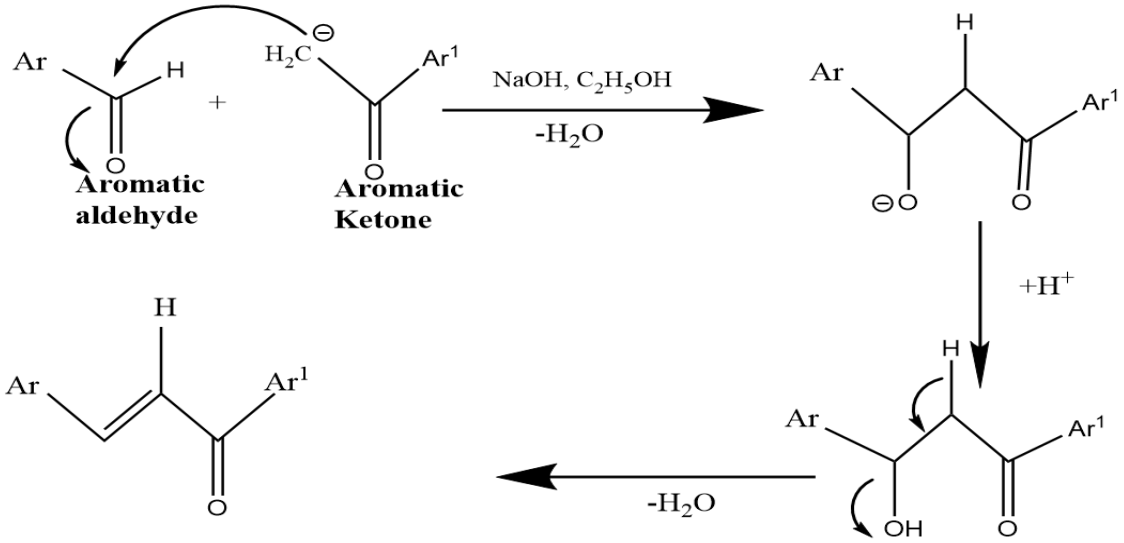


Fig.13

This conventional process has much more drawbacks such as Polar solvents required into this method; without the polar solvent the product was not formed. It's more time-consuming method. [5] Costly procedure. Yield value is not satisfactory in all cases.

Green synthetic methods for synthesis of chalcone:

Scheme 1: Chalcone synthesis by using solvent glycerine**[12]**

Glycerine is less polar solvent than water,now it's widely used as solvent for chalcone synthesis. Because by help of this solvent the yield value of product is more.The require amount of benzaldehyde derivatives and acetophenone derivatives were mixed together. Then added the dilute sodium hydroxide/potassium hydroxide solution into this solution mixture. At last glycerine was added like solvent into this reaction mixture. Then the reaction mixture was stirring into RT during 1-2 H. The yellow precipitate was fallen down under the reaction medium Then adding the hydrochloric acid solution for neutralized the reaction media and then it was filtered. Thus, the yellowish crude chalcone was prepared and recrystalized it by ethanolic solution.

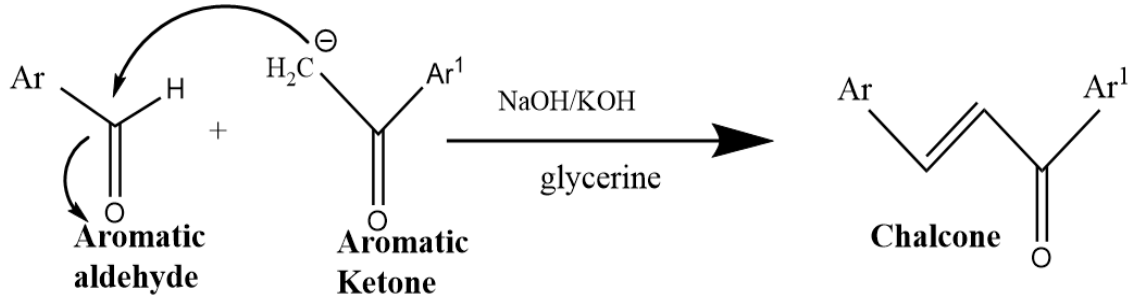


Fig.14

This process has much more advantages over conventional methods like that hence less time required than conventional synthesis, yield value is more than conventional synthesis.

Scheme 2: Chalcone synthesis by grinding method (Solvent free synthesis Procedure)**[13],[17]**

This method is most acceptable method into green chemistry because into conventional synthesis for chalcone huge amount of solvent is required but in case of grinding method no require of any solvent molecule.At first equivalent amount of methyl ketones and aldehyde derivatives were taken into porcelain mortar. Then added solid sodium hydroxide. Now this mixture was grinding for 3-5 minutes. Then the yellow solid mass materialized. This process was continued for an additional 5–10 minutes. By rinsing the crude products with frigid water, it was simple to separate them.Then this solution was filtered by Buchner funnel and recrystallization this product by proper solvent. Thus, the chalcone was prepared by grinding method.

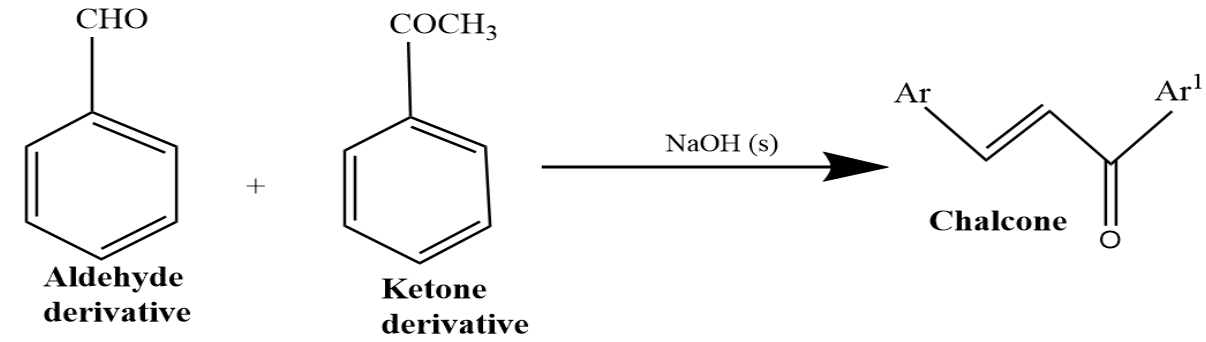


Fig.15

RCOCH3 + R'CHO → RCOCH=CHR'

The advantages of this process over conventional methods are excellent yield value, effective and simple process, short reaction time, solvent free reaction process and this reaction obeys the atom efficiency principles of green chemistry.

Scheme 3: Synthesis of chalcone by Nano catalyst:**[14]**

All compounds have unique specific surface area. This specific surface area is one of the main criteria for catalytic activity of every compound. Thus, a decrease in particle size coupled with an increase in the specific surface area per unit volume of the compound increases its catalytic activity. Nanocatalyst is a relatively new phenomenon in modern synthetic compounds. It defines as the materials which have nanoscale size, at least one-sided nanoscale dimension. Nanoscale enhance the catalytic activity.

Equimolar concentration of benzaldehyde and acetophenone were mixed together.Then added the nano catalysts like MCM-41-SO3H, CuNPs/C, copper ferrite (CuFe2O4) in this solution mixture. Then Stirred this solution continuously until the yellow colour precipitate was formed. Thus, the crude chalcone was prepared.Then the crude chalcone was purified by collum chromatography or recrystallization process.

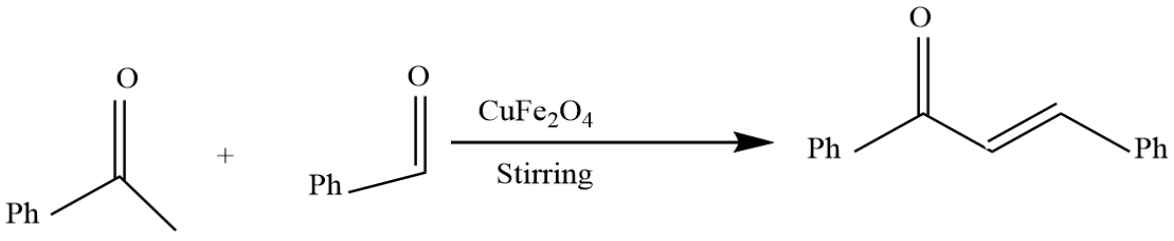
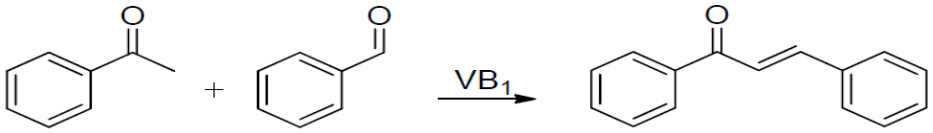


Fig.16

The Advantages of this methods over conventional methods are it's cost-effective process,yield value is very good than conventional process,[10]very little time is required for complete the reaction, Solvent free method, eco-friendly in nature and high efficacy, no by-products are formed in this process, obeys the catalysis principles of green chemistry, nanocatalysts are easily recoverable.

Scheme 4: Chalcone synthesis by thiamine hydrochloride (VB1)**[11], [16]**

Thiamine hydrochloride (VB1), is the important, powerful catalyst which use as many organic transformation reaction. It have two heterocyclic ring pyrimidine and thiazole moiety. It is a nontoxic and inexpensive reagent. Equimolar concentration of benzaldehyde derivatives was mixed into acetophenone derivatives. Then the thiamine hydrochloride was mixed into ethanol: water (v/v = 1:1) solvent. Now this mixture solution was added into previous aldehyde-ketonic solution. Now this solution mixture was reflux into reflux temperature. The yellow crude chalcone was formed into reaction medium. Then the solution was filtered by Buchner funnel.Thus, the crude chalcone was found and recrystallized it by proper solvent.



[15]

Fig.17

The advantages of this methods over conventional methods arethe reaction time is shorter than conventional process, additionally, no polar solvent is required and This reaction is occurred by metal free catalyst , so the reaction time is no longer.

Scheme 5: Chalcone synthesis by microwave assistance method**[11],[16]**

Microwave assistance method is very popular method for organic synthesis by green chemistry approach. Hence the product is form by microwave irradiation of reactants.At first equimolar concentration of active aldehydes and thiophene derivatives were taken into beaker. Then, a solution of ethanolic sodium hydroxide was added.Now, the reaction mixture was heated for 30–50 seconds in a microwave oven.The product was formed after the reaction mixture was chilled in an ice bath.Then, this solution was filtered and rinsed with ethanol and water until the media were neutral, and the crude product was recrystallized using ethanol and chloroform. Thus, the chalcone was formed.

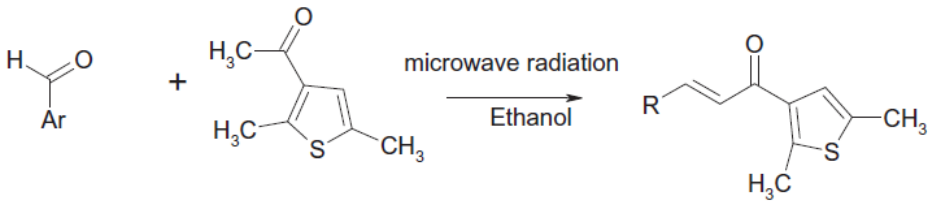


Fig.18

The advantages of this methods over conventional methods areit's most popular method for synthesis of chalcone by green chemistry approach, reaction time is much shorter than conventional process,[16,17]yield value is good.

Scheme 6: Chalcone synthesis by Ultrasound Irradiation :-**[11,17]**

Ultrasound waves is very common things for the diverse application in organic synthetic reaction. This waves increase the rate of reaction by lowering the activation energy.It is essential in synthetic organic chemistry because it reduces reaction temperature and time. At first the require amount of aromatic ketone and aromatic aldehyde mixed with dilute sodium hydroxide solution. Then this solution was maintained under ultrasonic irradiation in an ultrasonic cleaner's water bath at room temperature.This process was continued into 1-2 H. After this 1H the yellowish product was formed.Now this recrystalize the crude product.

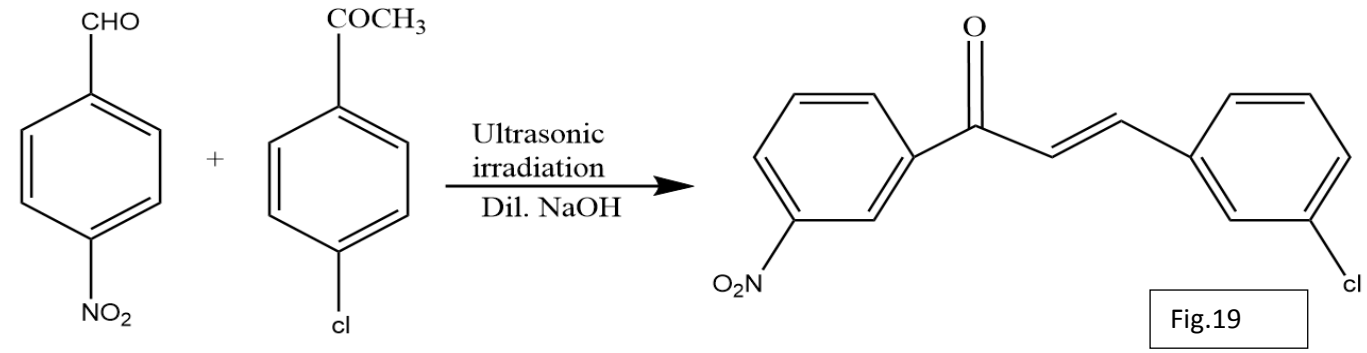


Fig.19

The advantages of this methods over conventional methods are temperature is not required reaction rate is high, little time is required, so it's not time-consuming process,yield value is excellent (90%).

Scheme 7: Chalcone synthesis by ionic solution:-**[11]**

Ionic liquids are a form of liquid containing a variety of cataions and anaions. They are the compounds that are liquid at temperatures below 100 degrees Celsius. These liquids are quite distinct from molten salts, which melt at greater temperatures. The first ionic liquid is Chloroaluminate, was invented in 1948. Synthetic ionic liquids include EMIM (1-ethyl-3-methylimidazolium) and BMIM (1-n-butyl-3-methylimidazolium).The require number of reactants was mixed with aqueous mediaThen 1-ethyl-3 methylimidazolium (EMIM) hydrogen sulphate (HSO4) ionic liquid was mixed into reaction media as a catalyst. Now reflux the full reaction media.After the complete of reaction media, the product was formed. Then recrystalise the crude product.

Fig.20

The advantages of this methods over conventional methodsare the reaction rate is marginally greater than conventional processes, this method is cost effective process, hence catalyst can be reused.[28]

Discussion:

In this review article we discussed about various green synthetic process for synthesis of chalcone and compared each green synthetic method with conventional method, at last finding which green synthetic method is most suitable for synthesis of chalcone.Hence every green synthetic method has various advantages over conventional method. Every green synthetic method obeys different principle of green chemistry. At first grinding method / solvent free method obey the atom efficiency principles of green chemistry. Into this reaction the amount of reactant molecules is equal to the amount of product molecules, so no loss of any reactant molecule. This method has various advantages over conventional method. Then chalcone synthesis by nano catalyst reaction obey catalysis principle of green chemistry. This catalyst increases the rate of reaction so the activation energy of this reaction will be low so the reaction quickly completed. Microwave assistance method obey the energy efficiency principles of green chemistry. Into this method the lowest amount of energy is required for complete the reaction. Ultrasonic irradiation method obeys design benign chemicals principles of green chemistry because hence no additionally solvent isn't required and no harmful chemicals are not use into this method. Chalcone synthesis by ionic solution method obeyuse of renewable feedstocks principle of green chemistry as here catalyst can be reused.

Conclusion:

For useful knowledge, potential ideas, and progress in a field of study, a current and pertinent literature review is essential. This review is a compilation and analysis of the literature on the significance of green chalcone synthesis, along with a discussion of the different benefits of green synthetic methods over traditional ones. This study emphasizes the value of using a green synthetic approach to create chalcone. This review emphasizes several green synthetic processes including grinding, using nanocatalysts, using microwaves to help, using ultrasound to irradiate materials, using ionic solutions, etc. The synthesis of chalcone using grinding and nanocatalysts is most suitable for this approach because it has a number of benefits, including excellent yield, selectivity, no by-products, high reactivity, solvent-free synthesis, short reaction times, fast workup, etc. Due to their high activity, selectivity, and productivity, nano catalysis has recently become a key tool in the synthesis of several organic compounds. This proposed review can serve as a source of cutting-edge knowledge for various green chalcone synthesis techniques.

References: -

[1] Mobinikhaledi,M.Kalhor,H.Jamalifar;"synthesis,characterization and antimicrobial activity of some novel bis-chalcones" Vol-2;"Medicinal Chemistry Research"**(June 2012)**; p.21:1811-1816. DOI 10.1007/s00044-011-9696-z

[2] Man Xu,Piye Wu,F. Shen, K.P.Rakesh;"Chalcone derivatives and their antibacterial activities" "Bioorganic chemistry" Elsevier USA;**(July 2019)**; p5-10. DOI 10.1016/j.bioorg.2019.103133

A. Shaik, R.Bhandare,K Palleapati,S.Shaik;"Various Biological activities of some novel Isoxazole Ring containing Chalcone and Dihydropyrazole derivatives" MDPI Publication;**(February 2020)** p.2-11.DOI :10.3390/molecules25051047

[3] S.Pola, K.Banoth, M.Sankaranarayanan,R.Ummani;"Design,synthesis and evaluation of novel chalcone and their naphthyl derivatives"; "Medicinal Chemistry Research"**(July 2020)**; DOI 10.1007/s00044-020-02602-8

[4] Samir Patel, Umang Shah;"Synthesis of flavones from acetophenone and aryl aldehyde derivatives by conventional and green chemistry approach" Vol-10,Issue-2 "Asian Journel of Pharmaceutical and Clinical Research" **(November 2017)** p.403-406.DOI 10.22159/ajpcr.2017.v10i2.15928

[5] J. Safaei-Ghomi, A. H. Bamoniri, M. Soltanian-Telkabadi; "A Modified andconvenient method for the preparation of N-phenylpyrazolinederivatives" Vol. 42, No. 7; "Chemistry of Heterocyclic Compounds"**(March 2006)**;p.892-897.

[6] R.Kumari,A.Varghese,L.George,Sudhakar.N;"Effect of solvent polarity on the photophysical properties of chalcone derivatives" "Royal society of chemistry"**(Febuary2017)**; p-24204-24206. DOI:10.1039/c7ra01705g

[7] Wijayanti.W.Lucia,Swasono.T.Respati,LeeWonkoo,JuminaJ; "Synthesis and evaluation of Chalcone derivatives as Nobel Sunscreen agent" "MDPI molecules" (**April 2021)** ; p-2-10. DOI:10.3390/molecules26092698

[8] K. S. Smuilovich, N. A. Orlova,E.V.Shakirov,V.V Shelkovnikov; "Reaction of polyfluorinated chalcones with hydrazine hydrate and phenylhydrazine" Vol-59,No-7; "Russian chemical Bulletin,International Edition"(**July 2010)** p.1408-1413; DOI:1066-5285/10.1039springer.

[9] X. Yunsheng,M.Jie,G.Xuedong, Y. Yihua; "An ab initio simulation of the UV/Visible spectra of substituted chalcones" "Central European Journal of Chemistry" **(April 2010)**; p.928-932; DOI:10.2478/s11532-010-0058-3.

[10] Dewi Septianingtyas, Nahda Zafira, Zulhipri, Fera Kurniadewi, Hanhan dianhar; "Green Synthesis of Chalcones Derivatives" "AIP Publishing" **(April 2021)**;p.040020_1-040020_7;DOI:10.1063/5.0042002.

[11] Mahesh G Kharatmol , Deepali M Jagdale; "Eco-Friendly Synthesis of Pyrazoline Derivatives" Vol-9,No-4; "International Journal of Pharmaceutical and Clinical Research" **(April 2017)**; p. 302-308; DOI: 10.25258/ijpcr.v9i04.8538.

[12] Marina Ritter, Rosiane M. Martins, Silvana A. Rosa, Juliana L. Malavolta,Rafael G. Lund, Alex F. C. Floresd, Claudio M. P. Pereira; "Green Synthesis of Chalcones and Microbiological Evaluation" Vol-26,No-6; "J. Braz. Chem. Soc."**(June 2015)**; p.1201-1210; DOI:10.5935/0103-5053.20150084.

[13] Nora M. Rateb & Hussein F. Zohdi; "Atom-Efficient, Solvent-Free, Green Synthesis of Chalcones by Grinding" "Synthetic Communications Taylor&Francis group" **(June2009)**;p.2789-2794; DOI:10.1080/00397910802664244

[14] Sapna Jain , Sanjeev Kumar , Bhawna Yadav Lamba , Jeevan Patra & Neeraj Mahindro "Nanocatalysts: Applications in synthesis of chalcones" "An International Journal for Rapid Communication of Synthetic Organic Chemistry" ; **(September 2020)** p.2132-2146; DOI: 10.1080/00397911.2020.1817941

[15] Huanhuan Yin, Ximeng Shi, Hao Wang, Guixia Liu and Lei Ma; "VB1 Promoted Green Synthesis of Chalcones and Its Neuroprotection Potency Evaluation" Vol-7; "MDPI Publication";**(April 2019)** p.2-14;DOI:10.3390/pr7040236.

[16] Salman A. Khan, Abdullah M. Asiri; "Green synthesis, characterization and biological evaluation of novel chalcones as anti-bacterial agents" "Arabian Journal of Chemistry, Elsevier"**(November 2013)** p.2-19; DOI:10.1016/j.arabjc.2013.11.018.

[17] Amole.K.L, Oyewale.O.A, Bello.A.I; "Mechanical solvent free synthesis and characterisation of new derivatives (E)-1-(2-hydroxyphenyl)-α-methyprop-2-en-1-one and their comparative study with conventional method" Vol-44,No.2 "J.Chem.Society Nigeria" **(March 2019)** ;p.245-255.DOI:10.1386/jc2105n

[18] Salehi B, Quispe C, Chamkhi I, et al. Pharmacological Properties of Chalcones: A Review of Preclinical Including Molecular Mechanisms and Clinical Evidence. *Frontiers in Pharmacology*. 2021;11:592654. doi:10.3389/fphar.2020.592654

[19] Garcia AR, Oliveira DMP, Jesus JB, et al. Identification of Chalcone Derivatives as Inhibitors of Leishmania infantum Arginase and Promising Antileishmanial Agents. *Frontiers in Chemistry*. 2021;8. doi:10.3389/fchem.2020.624678

[20] Gupta D, Jain D. Chalcone derivatives as potential antifungal agents: Synthesis, and antifungal activity. *Journal of Advanced Pharmaceutical Technology & Research*. 2015;6(3):114. doi:10.4103/2231-4040.161507

[21] Mendanha D, Vieira de Castro J, Moreira J, et al. A New Chalcone Derivative with Promising Antiproliferative and Anti-Invasion Activities in Glioblastoma Cells. *Molecules*. 2021;26(11):3383. doi:10.3390/molecules26113383

[22] Moreira J, Almeida J, Saraiva L, Cidade H, Pinto M. Chalcones as Promising Antitumor Agents by Targeting the p53 Pathway: An Overview and New Insights in Drug-Likeness. *Molecules*. 2021;26(12):3737. doi:10.3390/molecules26123737

[23] Gacche RN, Dhole NA, Kamble SG, Bandgar BP. *In-vitro* evaluation of selected chalcones for antioxidant activity. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2008;23(1):28-31. doi:10.1080/14756360701306370

[24] Jaiswal S, Shukla M, Sharma A, et al. Preclinical pharmacokinetics and ADME characterization of a novel anticancer chalcone, cardamonin. *Drug Testing and Analysis*. 2016;9(8):1124-1136. doi:10.1002/dta.2128

[25] Stevens, J.M.; Taylor, A.M.; Nickerson, G.B.; Ivancic, M.; Henning, J.; Haunold, A.; Deinzer, M.L. Prenylflavonoid variation in Humulus lupulus: Distribution and taxonomic significance of xanthogalenol and 40 -O-methylxanthohumol. Phytochemistry **(June2000)**, 53, 759–775

[26] Shao, Z.K.; Wang, L.J.; Liu, S.; Wang, X.F. Tetramethylpyrazine Protects Neurons from Oxygen-Glucose Deprivation-Induced Death. Death. Med. Sci. Monit. **(April 2017)**, 23, 5277–5282.

[27] Kakati, D.; Barua, N.C. Total synthesis and assignment of the absolute stereochemistry of xanthoangelol. Development of a highly efficient method for Claisen–Schmidt condensation. Tetrahedron **(May 2014),** 70, 637–642.

[28] Martins, M. A. P.; Pereira, A. M. P.; Cunico, W.; Moura, S.; Rosa, F. A.; Peres, R. L.; Machado, P.; Zanatta, N.; Bonacorso, H. G.; Ultrason. Sonochem. (2006), 13, 364.

[29] Rizvi, S. U. F.; Siddiqui, H. L.; Parvez, M.; Ahmad, M.; Siddiqui, W. A.; Yasinzai, M. M.; Chem. Pharm. Bull. 2010, 58, 301

[30] Nowakowska, Z.; Kedzia, B.; Schroeder, G. Synthesis, physicochemical properties, and antimicrobial evaluation of new (E)–chalcones. Eur. J. Med. Chem. 2008, 43, 707–713.

[31] Szliszka E, Czuba ZP, Domino M, Mazur B, Zydowicz G, Krol W. Ethanolic Extract of Propolis (EEP) Enhances the Apoptosis- Inducing Potential of TRAIL in Cancer Cells. *Molecules*. 2009;14(2):738-754. doi.org/10.3390/molecules

[32] Lagu SB, Yejella RP, Bhandare RR, Shaik AB. Design, Synthesis, and Antibacterial and Antifungal Activities of Novel Trifluoromethyl and Trifluoromethoxy Substituted Chalcone Derivatives. *Pharmaceuticals*. 2020;13(11):375. doi.org/10.3390/ph13110375

[33] Chen G, Zhou D, Li XZ, et al. A natural chalcone induces apoptosis in lung cancer cells: 3D-QSAR, docking and an in vivo/vitro assay. *Scientific Reports*. 2017;7(1). doi.org/10.1038/s41598-017-11369-9

[34] Kurt BZ, Ozten Kandas N, Dag A, Sonmez F, Kucukislamoglu M. Synthesis and biological evaluation of novel coumarin-chalcone derivatives containing urea moiety as potential anticancer agents. *Arabian Journal of Chemistry*. 2020;13(1):1120-1129. doi.org/10.1016/j.arabjc.2017.10.001

[35] Balasubramanian R, Iqbal H, Vijaya Gopal R, Baby C. Synthesis and preliminary evaluation of a focused chalcone library for anti-inflammatory activity. *Indian Journal Of Pharmaceutical Education And Research*. 2014;47(4):31-38. doi.org/10.5530/ijper.47.4.5

[36] Suwito H, Jumina, Mustofa, et al. Design and Synthesis of Chalcone Derivatives as Inhibitors of the Ferredoxin — Ferredoxin-NADP+ Reductase Interaction of Plasmodium falciparum: Pursuing New Antimalarial Agents. *Molecules*. 2014;19(12):21473-21488. doi.org/10.3390/molecules191221473

[37] Bui TH, Nguyen NT, Dang PH, Nguyen HX, Nguyen MTT. Design and synthesis of chalcone derivatives as potential non-purine xanthine oxidase inhibitors. *SpringerPlus*. 2016;5(1). doi.org/10.1186/s40064-016-3485-6

[38] Bhale PS, Chavan HV, Dongare SB, et al. Synthesis of extended conjugated indolyl chalcones as potent anti-breast cancer, anti-inflammatory and antioxidant agents. *Bioorganic & Medicinal Chemistry Letters*. 2017;27(7):1502-1507. doi.org/10.1016/j.bmcl.2017.02.052

[39] Stepkina NN, Velikorodov AV. DEPENDENCE OF BIOLOGICAL ACTIVITY OF CHALCONES ON THEIR STRUCTURE. *Фундаментальные исследования (Fundamental research)*. 2015;1(№ 11 2015). doi.org/10.17513/fr.39449

[40] El-Messery SM, Habib ESE, Al-Rashood STA, Hassan GS. Synthesis, antimicrobial, anti-biofilm evaluation, and molecular modelling study of new chalcone linked amines derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2018;33(1):818-832. doi.org/10.1080/14756366.2018.1461855

[41] Bennani FE, Doudach L, Cherrah Y, et al. Overview of recent developments of pyrazole derivatives as an anticancer agent in different cell line. *Bioorganic Chemistry*. 2020;97:103470. doi:https://doi.org/10.1016/j.bioorg.2019.103470

[42] Semenok D, Kletskov A, Dikusar E, Potkin V, Lukin O. Efficient synthesis of chalcone-4′-sulfonyl chlorides and fluorides. *Tetrahedron Letters*. 2018;59(4):372-374. doi.org/10.1016/j.tetlet.2017.12.044

[43] Li Z, Zhao H, Han H, et al. Graphene-supported ZnO nanoparticles: An efficient heterogeneous catalyst for the Claisen-Schmidt condensation reaction without additional base. *Tetrahedron Letters*. 2017;58(42):3984-3988. doi.org/10.1016/j.tetlet.2017.09.011

[44] Illicachi L, Montalvo-Acosta J, Insuasty A, et al. Synthesis and DFT Calculations of Novel Vanillin-Chalcones and Their 3-Aryl-5-(4-(2-(dimethylamino)-ethoxy)-3-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbaldehyde Derivatives as Antifungal Agents. *Molecules*. 2017;22(9):1476. doi.org/10.3390/molecules22091476