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QUERCETIN LOADED POLY VINYL ALCOHOL- ALGINATE HYDROGEL ATTENUVATES INFLAMMATION

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ABSTRACT: The flavonoid compound quercetin is widely acknowledged for its diverse biological properties including anti-inflammatory, antioxidant, anti-bacterial, anti-ageing, anticancer however the constraints like poor solubility, low bioavailability, lack of stability and decreased permeability limits its pharmacological applications. Hydrogel assisted delivery systems especially for transdermal delivery of phytochemicals like quercetin is being suggested but least explored for its efficacy as an anti-inflammatory system. A PVA - alginate system was synthesized with quercetin and was explored for its effect as a potent anti-inflammatory system. The synthesized hydrogel was found to exhibit 56% loading efficiency and shown a sustained release over time as determined using HPLC analysis. The hydrogel system exhibited appreciable inhibition of total COX, 5 LOX, iNOS activity, Nitrate levels and MPO activity in RAW macrophage cells when compared with LPS alone treated groups affirming anti-inflammatory potential which can find applications in development of therapeutic regimens which will emphasize an economical, highly effective and risk-free plant drug with minimum side effects.

INTRODUCTION: Inflammation is a pervading phenomenon which can be generally defined as a sequence of response evoked by body's immune system as a protective mechanism against certain stimulation including endogenous signals resulting from tissue injury as well as exogenous stimuli from infecting pathogens and its corresponding pathologies. The elicited responses are characterised by the presence of pain, redness and rashes, and when goes unchecked these can lead to harmful consequences induced by the by-products of inflammatory cascade [1].

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Inflammatory responses have a key role in the development of various diseases including cancer; they also interfere with immunosurveillance and response to treatment [2]. The traditional therapeutic strategies are limited to the effort to minimize the symptoms of the response. Recently, with the development Sustained Release Drug Delivery System formulated to release drugs at a constant level for a specific time period at a fixed rate with minimum side effects, are becoming the centre of attraction for the treatment of inflammation related diseases [3].

The main aim of sustained drug delivery systems are to alter and enhance the drug performance by varying factors like duration of drug action, dosing frequency and amount, *etc.*, thus modifying them to be an efficient therapeutic agent [4]. The ability to deliver phytochemical to sites of inflammation with sustained release can overrule the limitations of

phytotherapy in a significant manner. Quercetin, a well-known antioxidant, described to be present many traditional and culinary plant materials [5] is classified into a group of plant pigments called flavonoids [6], and is reported to have powerful and long lasting anti-inflammatory [7] ability like inhibiting production of LPS induced TNFα, Interleukin1α, inhibition of inflammation inducing enzymes like cycloxygenase and lipoxygenase *etc*., But pharmacokinetic trails indicate poor oral bioavailability of Quercetin in humans, which will considerably reduce the desired applicability of the compound [8]. The application of biopolymers for delivery of phytochemicals like quercetin is widely accepted for its low toxicity, biocompatibility biodegradability, stability and renewable nature [9].

Researchers are in search of hydrogels based on different matrix (natural and synthetic) to meet different biomedical applications such as controlled and sustained drug delivery systems. Due to the major properties of hydrogels (hydrophilicity, biocompatibility, sensitivity to the physiological changes and ductility) make them as a suitable choice for various biomedical applications [10]. Upto the present time, for the fabrication of polymer-based hydrogels system, gelatin, collagen, sodium alginate, PEG and PVA have been widely utilized. In our present study PVA/ Sodium alginate-based hydrogel system was fabricated for the sustained release of quercetin. PVA/ Sodium alginate based hydrogels have been known as promising candidate for biomedical applications due to its several characteristic features (non-toxicity, biodegradability, biocompatibility and high hydrophilicity) [11].

MATERIALS AND METHODS:

Chemicals: Quercetin (Product Code: Q4951) was purchased from Sigma Aldrich. Dihydrogen orthophosphate, disodium hydrogen orthophosphate, bovine serum albumin (BSA), *L*-cysteine and other chemicals of analytical grade were obtained from Sigma Aldrich, St. Louis, USA. DMEM, trypsin, antibiotics and the other chemicals were procured from Gibco, Invitrogen (USA).

Cell Lines: RAW 264.7 was procured from National centre for cells sciences (NCCS), Pune, India, which was maintained in Dulbecco's modified eagle medium (After trypsinization, the cells were suspended in growth medium (10% FBS) and cell suspension was seeded to corresponding plates and incubated at 37^0C in a humidified CO_2 incubator (NBS Eppendorf, Germany) with 5% CO_2.

Preparation of Quercetin Incorporated Biopolymer: Biopolymer was prepared by cross-linking polyvinyl alcohol (PVA) and alginate. 1% PVA solution containing 1mg/ml Quercetin was stirred continuously for 5-6 hours in a magnetic stirrer to form a homogeneous solution. 1% alginate solution was added along and continued stirring overnight. The solution mixture was further casted to form thin membrane, dried and was cured using 0.2mM Calcium chloride solution. The clear dried membrane was cut into 10mm discs and served as Quercetin incorporated Hydrogel (QHg). The membrane without the incorporation of Quercetin was prepared using similar methodology and employed as control Hydrogel (CHg).

Release Kinetics Study of Quercetin: The release kinetics and encapsulation efficiency of QHg was determined using HPLC technique. HPLC analysis was carried out in Agilent-1260 series HPLC system (Agilent Technologies, Palo Alto, CA, USA) and the separation was performed on Zorbax Eclipse plus C18 column (column specification: 3.5 um, 100 mm X4.6 mm, Agilent). Mobile phase used was Methanol- 0.1% O-phosphoric acid (65:35) at a flow rate of 1.0 mL/min and chromatograms were recorded at wavelength 369 nm. The concentration of Quercetin was calculated from the peak areas of chromatogram.

Anti-inflammatory Activity of Fabricated Hydrogel Incorporated with Quercetin: 60% confluent RAW 264.7 macrophage cell lines were induced with 1µL LPS (1µg/mL) and exposed to QHg, CHg and standard Quercetin alone for 24 hrs. After incubation the cells were observed under inverted phase contrast tissue culture microscope (Olympus CKX41 with Optica pro 5CCD camera) for morphological changes and imaged.

Cycloxygenase (COX) Activity: COX activity was assayed by the method of Walker and Gierse, 2010 [12]. The cell lysate was incubated at 25°C for 1 minute in Tris-HCl buffer (pH 8), containing

glutathione 5mM/L, and hemoglobin 5 mM/L; was added with arachidonic acid 200 mM/L, for initiating reaction; was added with10% trichloroacetic acid in 1 N hydrochloric acid and was incubated it at 37°C for its termination after 20 minutes. Supernatant was added with 1% thiobarbiturate and kept for 20 minutes in boiling water bath. COX activity was determined by reading absorbance at 632 nm. The absorbance was read at 632nm and percentage inhibition of COX activity was determined as per the following equation.

COX inhibition (%) = (Mean OD of control - Mean OD of test)) / (Mean OD of control) × 100

5-LOX Activity: LOX activity was then determined as per method of Axelrod *et al*, 1981[13]. 2 mL reaction mixture containing Tris-HCl buffer (pH 7.4), sodium linoleate (200 µL) and 50µL of cell lysate was monitored for 5-hydroxyeicosatetraenoic acid formation as an increase of absorbance at 234 nm, which was related to LOX activity. Percentage inhibition of the enzyme was then calculated using the formula as mentioned below.

LOX inhibition (%) = (Mean OD of control-Mean OD of test)) / (Mean OD of control) ×100

MPO Activity: MPO activity was further determined using Graff *et. al.,* (1998). MPO in the sample was activated by adding of 50 mM phosphate buffer (pH 6) with 1.67 mg/mL guaiacol and 0.005% H_2O_2. Difference in absorbance at 460 nm was further measured which was correlated to MPO activity as units per mL of cell lysate.

Estimation of Ions: iNOS was determined based on the method of Salter *et.al.*, (1991) [14]. Equal amount of cell lysate (100µL) was added with HEPES reagent **(**0.1mL *L*- Arginine, 0.1mL manganese chloride, 0.1mL 30µg dithiothreitol (DTT), 0.1mL NADPH, 0.1mLtetrahydropterin, 0.1mL, oxygenated haemoglobin). The absorbance was read at 490 nm (Agilent Cary 60) at the 0^{th} and 5^{th} minutes.

Estimation of Cellular Nitrate Level: Cellular nitrate level was done by the method of Lepoivre *et.al.,* (1990) [15]. 0.5 mL of cell lysate was added with 0.1 mL of sulfosalicylic acid, vortexed for 30 minutes, 200 µL protein-free supernatant obtained by centrifuging was mixed with 30 µL of 10% NaOH, followed by 300 µL of Tris-HCl buffer and mixed well and added 530 µL of Griess reagent (1% sulphanilamide; 0.1% N-(1-Naphthyl) ethylenediamine (NED) and 6% phosphoric acid) and incubated in the dark for 15 minutes. The absorbance was read at 540 nm against Griess reagent as blank.

RESULTS: In consideration with the strong antioxidant and anti-inflammatory ability of Quercetin and its poor pharmacokinetic properties remains a limitation in using for therapeutic regimens. We attempted to develop Hydrogel, loaded with Quercetin; QHg, by cross linking PVA- Alginate and to determine its applicability as an Anti-inflammatory polymeric coating. The biopolymer without Quercetin served as the control (CHg) **Fig. 1A** and the biopolymer with Quercetin served as the test sample (QHg) **Fig. 1B.**

Control Biopolymer Quercetin Loaded Biopolymer

FIG. 1: FABRICATED BIOPOLYMER (A) HYDROGEL WITHOUT QUERCETIN (B) FABRICATED HYDROGEL INCORPORATED WITH QUERCETIN

Encapsulation efficiency and Release kinetics of QHg has shown significant results **Fig. 4A**. From the chromatogram obtained, the amount of Quercetin encapsulated was found to be 43.33 ppm and the encapsulation efficiency was calculated as 56.7% **Fig. 2.**

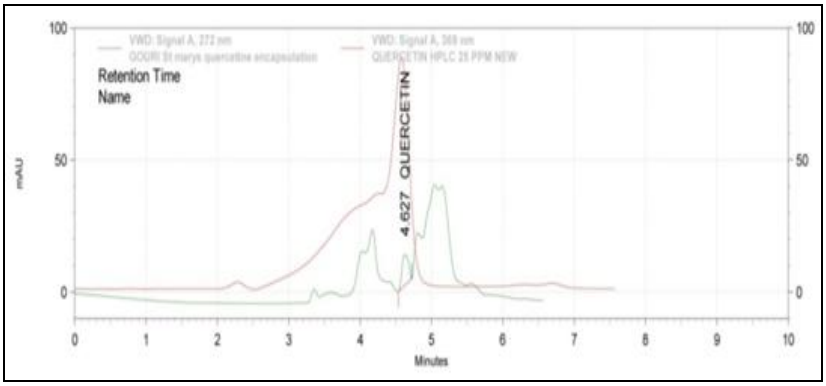

FIG. 2: HPLC CHROMATOGRAM FOR CHECKING THE ENCAPSULATION CAPACITY

Further for determining the toxicity effect and Anti-inflammatory activity of biopolymer, LPS induced RAW 264.7 macrophage cell lines were seeded on Quercetin incorporated biopolymer (QHg) and Control Biopolymer (CHg) **Fig. 3**. The anti-inflammatory efficiency of the QHg and CHg, was substantially analysed on LPS induced RAW 264.7 macrophage cell lines for determining its efficiency as an anti-inflammatory coating. After incubation, the cells were observed under an inverted phase contrast tissue culture microscope and the microscopic images confirmed the intensity of damages was reduced in the cells induced with LPS, treated with QHg, when compared to LPS control.

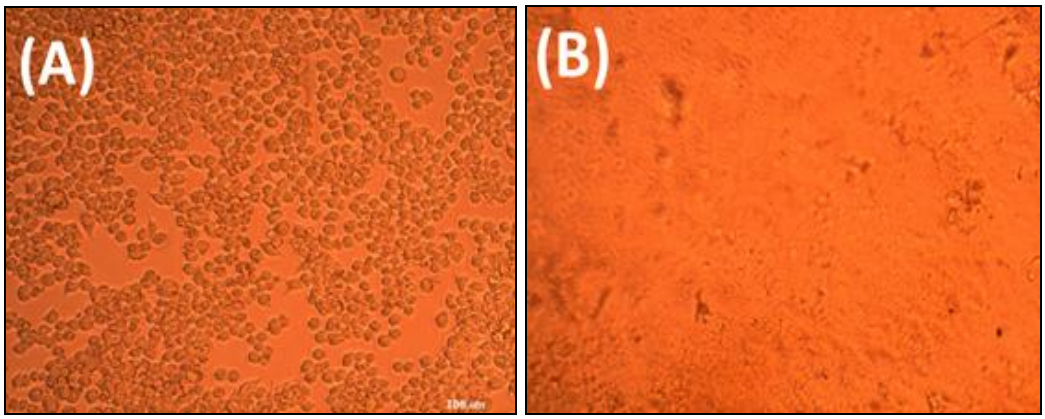

FIG. 3: PHASE CONTRAST MICROSCOPIC IMAGES OF (A) LPS INDUCED CELLS (B) LPS INDUCED CELLS TREATED WITH QHG

COX, LOX, iNOS, MPO and cellular nitrate levels are all major mediators of inflammation. Monitoring these mediators and targeting their activity can provide insights into the anti-inflammatory effects of interventions or substances. Inorder to check the anti-inflammatory activity of the fabricated hydrogel incorporated with quercetin all the above-mentioned mediators were evaluated.

COX is the major enzyme responsible for the production of pro inflammatory molecules which are collectively known as prostaglandins, whereas LOX enzymes are another major group of enzymes involved in the production of inflammatory molecules called leukoterins. COX and LOX **Fig. 4B and 4C** activity was found to be inhibiting significantly in the cells induced with LPS treated with QHg when compared with Quercetin alone and cells treated biopolymer without Quercetin (CHg) induced with LPS. The observation showed the ability of QHg to down regulate the prostaglandin synthesis in which COX is involved and production of leukotrienes involving LOX, ultimately protecting the cells against development of inflammation signals.

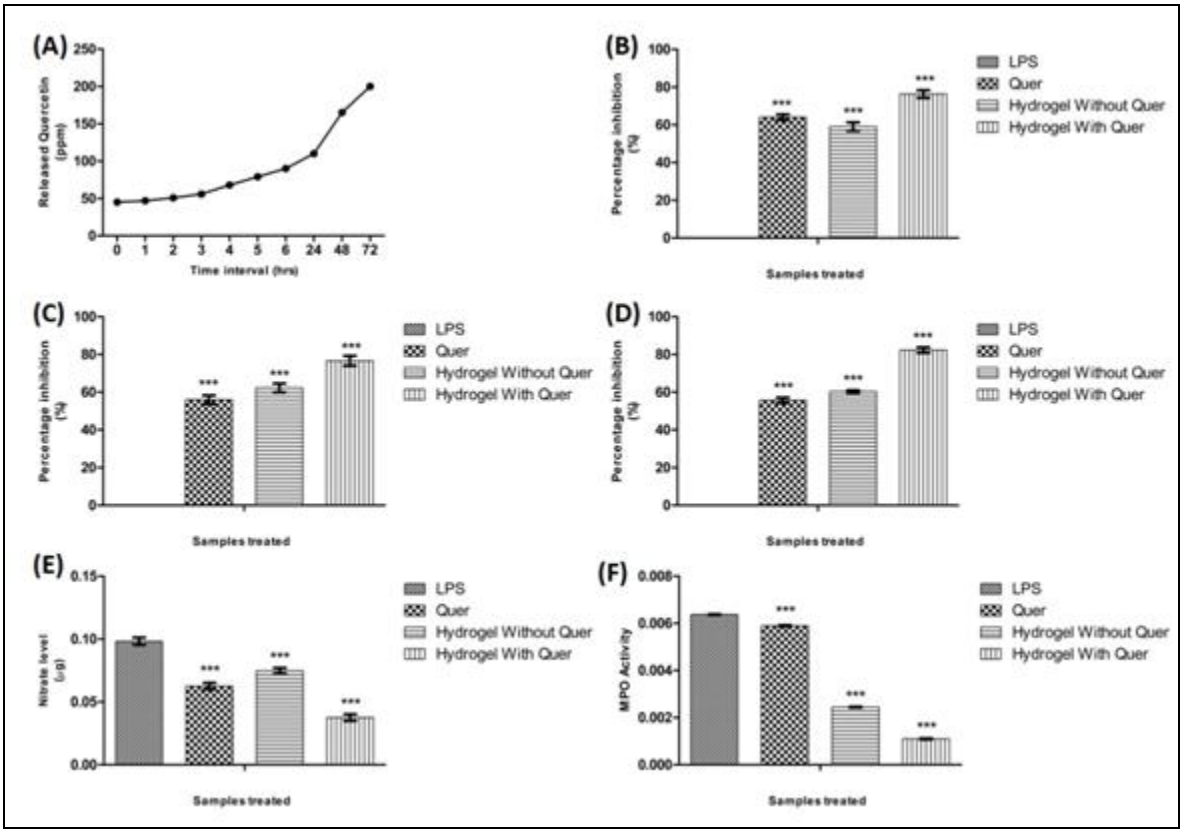

FIG. 4: GRAPHICAL REPRESENTATION ILLUSTRATING (A) THE AMOUNT OF QUERCETIN RELEASED FROM THE FABRICATED HYDROGEL ON DIFFERENT TIME INTERVALS (B) COX INHIBITORY ACTIVITY (C) LOX INHIBITORY ACTIVITY (D) INDUCIBLE NITRIC OXIDE SYNTHASE (E) CELLULAR NITRATE LEVEL (F) MYLOPEROXIDASE ACTIVITY

MPO is the major enzyme which is found in the immune cells, particularly neutrophils, which plays and role in the oxidative burst during inflammation by generating reactive oxygen species which leads to tissue damage and finally inflammation. In case of iNOS, a signalling molecule involved in production of nitric oxide in response to inflammation which may damage tissue. While determining myeoloperoxidase activity and iNOS activity, the inhibition was found to be decreasing in LPS induced cells treated with QHg when compared to CHg and quercetin alone **Fig. 4D** and **4F.** Cellular nitrate is a metabolite of nitric oxide which will be in an elevated condition during inflammation. The intracellular nitrite level estimation showed less accumulation of nitrite in the cells treated with QHg when compared to CHg and quercetin alone **Fig. 4E**. The observation indicated decreased amount of oxidative damage in the respective cells.

DISCUSSION: Nature provides an equitable system which delivers its constituting elements balanced and sustainable life. Countless phyto-constituents are explored and extracted from diverse natural sources which are pharmacologically underexplored but are described to have innumerable therapeutical applications [16].

Quercetin, a natural antioxidant which cannot be synthesized by human body [17]; and are reported to have various biological activity like anti-inflammatory [18, 19], antioxidant [7], psycho-stimulant activities [20], anticancer [21], even anti-aging [22, 23] properties and several others are proved by many authors using *in-vivo* and *in-vitro* experiments [21].

Quercetin is aglycone compound, devoid of an attached sugar and is found as yellow needle shaped crystals, with poor/ no water solubility [24], thus limiting its therapeutical application and also due to its poor bioavailability, instability and low permeability [25]. The major inhibiting factor is its metabolical clearance once ingested however the mechanism behind which is still unknown [26, 27]. These disadvantages thus prompt the development of better carriage systems for the proper delivery of Quercetin to its targeted metabolic system without

affecting or altering its biological properties. In this aspect the present study was designed to establish a biopolymer loaded with Quercetin (QHg) and to validate it's the anti inflammatory activity o on LPS activated macrophage cells, using RAW 264.7 macrophage cell lines as *in-vitro* model using various experimental analyses.

Hydrogel was prepared by crosslinking PVA-Alginate system to provide a proper delivery system for the appropriate distribution of Quercetin. Polyvinyl alcohol (PVOH) is a polymer normally used in food packaging owing to its non toxic effect [28]. It is a synthetic hydrophilic linear polymer that generally exists as a copolymer of vinyl alcohol and vinyl acetate and is known to have elastic nature in swollen state, high water content, and relatively safe when administered orally (LD_{50}) in rats and mice are more than 20 g/kg and 14.7 g/kg, respectively [29]. These properties make PVOH hydrogels a novel candidate as tissue replacement material. The PVOH hydrogels have been studied vastly for its application as artificial heart linings, soft contact lens material, catheters, artificial cartilages, artificial skin, and pancreas membranes [30] and in the present study we used calcium alginate cross linked PVA biopolymer system for the delivery of Quercetin.Small matrices of calcium alginate has been investigated in some studies to analyse its possibility as controlled release systems for drugs [31].

The potential of PVA- alginate membrane to hold Quercetin was then determined in terms of encapsulation efficiency and from our results it was observed that the biopolymer holds a significant encapsulation efficiency of 56.7% when determined by HPLC analysis. Further analysis of release kinetic by HPLC analysis has shown sustained release kinetics up to 72 hours of incubation which is quite impressive as per previous findings [32].

The anti inflammatory potential of biopolymer encapsulated Quercetin were checked in RAW 264.7 macrophages cell lines induced with LPS and our results were consistent in proving the efficiency of biopolymer to reduce the expression of inflammatory markers and enzymes. There was a significant inhibition of cyclooxgenase and lipooxygenase activity in biopolymer loaded with Quercetin when compared with Quercetin alone and biopolymer alone.

COX, 5-LOX inhibitors are now considered as novel potential drugs to treat inflammation. Cyclooxygenase (COX) is one the key enzymes in the anabolism of prostaglandin (PG), and plays an important role in controling the major pathways of arachidonic acid metabolism. On the other hand, emerging information has appreciated the role of other arachidonic acid metabolic pathway the 5-lipoxygenase (5-LO) pathway) in producing and maintaining inflammation. Moreover, it is now being perceived that COX-2 and 5-LO have converging functions not only in inflammation but also in cell proliferation and neo-angiogenesis [33]. In this regard, there is evidence that COX-2 and 5-LO are co-expressed and up-regulated in a number of inflammatory and neoplastic disorders, and that COX-2 as well as 5-LO inhibitors have beneficial effects in inflammatory diseases and sustained release of Quercetin has resulted in inhibition of both COX and 5-LOX which can be considered significant on a therapeutic viewpoint.

Further to that there was significant decrease in myleoperoxidase activity, iNOS activity and the net nitrate concentration in cells treated with Quercetin encapsulated biopolymer over free Quercetin and control biopolymer.

It was of our concern to depict the effect of QHg on LPS induced RAW cells in the expression of nuclear factor NF-κB which exists in the cytoplasm in an inactive form associated with regulatory proteins called inhibitors of κB (IκB). NF-κB pathway is a prototypical proinflammatory signaling pathway. NF-κB is one of the most important regulators of proinflammatory gene expression and plays a central role in inflammation [34]. Hence, it can be concluded that Quercetin encapsulated PVA alginate biopolymer system can be a potent therapeutic intervention for treating inflammatory diseases and disorders.

CONCLUSION: Hydrogel properties need to be optimized for developing advanced drug delivery systems and biological properties including safety, biodegradability, drug loading capacity, and control on drug release kinetics makes hydrogel a potent

delivery system. In the present study the anti inflammatory activity of poly vinyl alcohol – sodium alginate biopolymer system incorporated with Quercetin was studied in detail for anti inflammatory potential. PVA- alginate biopolymer system was synthesized using polymerization using calcium chloride and was loaded with Quercetin. The encapsulation efficiency was determined to be 56% and the gel system exhibited a sustained release when determined by HPLC analysis. Protein denaturation and proteinase inhibition was inhibited by presence of Quercetin loaded hydrogel system. RAW 264.7 macrophage cells were activated with LPS and presence of Quercetin loaded PVA alginate produced significant decrease in COX, LOX, MPO and nitrate levels.

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CONFLICTS OF INTEREST: Nil

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