Effect of Different Additives on the Mechanical Properties of Gelatin Methacryloyl Hydrogel: A Meta-analysis

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ABSTRACT: Gelatin methacryloyl (GelMA) hydrogel has adjustable physicochemical properties and a three-dimensional network structure for cell growth and hence a hot issue in the field of tissue engineering. However, its poor mechanical properties limit the application in the scaffold, especially as a bone scaffold. To date, many research studies have been carried out by adding some additives into GelMA to construct GelMA-based composites to improve the mechanical properties. However, there is a controversy as to whether the additives can improve the mechanical properties of GelMA. Herein, meta-analysis was used to evaluate the influence of the additives on the mechanical properties of GelMA-based composites, which can provide reference for the further enhancement of mechanical properties of GelMA. In this study, meta-analysis was adopted to investigate the influence of additives on the mechanical properties of GelMA composites; composites with different concentrations of GelMA, that is, ≥10% (w/v), 5–10% (w/v), and ≤5% (w/v) were found in 23 literatures and heterogeneity could be found among these references. Accordingly, it is found that additives can improve the mechanical properties in each concentration.

1. INTRODUCTION

Bone defects and bone injuries from various causes have been serious world health problems.1,2 Clinically, autogenous bone graft is the gold standard of treatment; however, transplantation of the autologous bone for its limited source is likely to cause secondary damage to the donor bone area during sampling. In addition, there are risks such as high infection rate and immune rejection in allogeneic bone transplantation. Therefore, it is of great significance to construct a suitable vector by bone tissue engineering technology, so that the cells can stick to it and grow into a new bone.1,3

Ideal bone tissue engineering scaffold materials should have good biocompatibility, mechanical properties, biological activity, adaptability to cell growth, and so forth.1 Gelatin methacryloyl (GelMA) hydrogel has good biocompatibility and permeability and adjustable physical and chemical properties, especially a three-dimensional network structure suitable for cell growth, which is conducive to cell adhesion and reconstruction.5,6 Therefore, GelMA hydrogel has been widely used in the field of tissue engineering, such as bone,7 endochondral bone,10 heart tissue,11,12 cartilage,13–15 vascular network,16 cornea,17 and so forth. GelMA has been applied in bone tissue engineering. However, the disadvantage of GelMA as a scaffold for bone tissue process is its poor mechanical properties (the compressive modulus of a human trabecular bone is 50–50018 and 2–12 MPa;19 the stiffness range of a native spongy bone is 55–480 MPa20), which limits its application.21 In order to improve the mechanical properties of GelMA, one method is to change the synthetic parameters of the GelMA hydrogel (such as acylation, photocrosslinking conditions, etc.).6,22,23 However, GelMA hydrogels derived from these methods tend to be damaged. Noshadi24 found that UV caused accelerated tissue aging or cancer, and the combination of both UV light and the photoinitiator Irgacure2959 resulted in harmful effects on cell viability.25,26 Hence, adding additives to GelMA, structuring GelMA-based composites, is a desirable way to improve the mechanical properties of the GelMA hydrogel.21

There have been a lot of reports about GelMA-based composite research. The additives in the GelMA-based composites include hyaluronic acid-methacrylamide (HAMA),27,28 poly(ethylene glycol) diacrylate (PEGDA),29 nanoparticles (NPs),30 carbon nanotubes (CNTs),31,32 and so forth. Whether the synthetic composites can improve the mechanical properties of GelMA is controversial in different references. In view of the above mentioned reasons, meta-analysis can play an important role in this issue. Meta-analysis can be synthetically and systematically
Table 1. Article Search Terms: 15 Search Criteria Keywords Phrasesa

| group | keywords phrases |
|-------|------------------|
| 1     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (mechanical parameters) |
| 2     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (mechanical properties) |
| 3     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (mechanical strength) |
| 4     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (modulus) |
| 5     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressibility) |
| 6     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive) |
| 7     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 8     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 9     | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 10    | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 11    | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 12    | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 13    | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 14    | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |
| 15    | (gelatin methacrylate) OR (methacrylated gelatin) OR (methacrylamide modified gelatin) OR (gelatin methacrylamide) OR (gelatin methacryloyl) OR (GelMA) AND (compressive modulus) |

Finally, taking the 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 as the final retrieval scheme.

Table 2. Basic Data of Included 23 Literatures (Including the First Author, Additives, the Experimental Group GelMA-Based Composites, and the Control Group Pure GelMA)

| the first author (published year) | additives | the experimental group | the control group |
|----------------------------------|-----------|------------------------|------------------|
| Shirazi (2016)                   | 0.3 mg mg⁻¹ bioactive glass (BG) and 100 mg mL⁻¹ poly(ethylene glycol) diacrylate (PEGDA) | GelMA−BG−PEGDA−BG | GelMA |
| Moghanian (2020)                 | 10% (w/v) a modified strontium-and lithium-doped 58S BG (BG-5/5) 20% (w/v) a modified strontium-and lithium-doped 58S BG (BG-5/5) polycrylamide (PAA) [AA/GelMA = 0.4(w/w)] 1% (w/v) alginate-methacrylate (AlgMA) 1% (w/v) carboxymethyl cellulose-methacrylate (CMCMA) 1% (w/v) poly(ethylene glycol) diacrylate (PEGDA) | GelMA/BG-5/5 (10% BG-5/5) GelMA/BG-5/5 (20% BG-5/5) GelMA−PAA GelMA−AlgMA GelMA−CMCMA GelMA−PEGDA | GelMA |
| García-Lizarribar (2018)        | 0.1% (w/v) poly(3,4-ethylenedioxythiophene):poly(styrene sulfonate) (PEDOT:PSS) 0.3% (w/v) PEDOT:PSS | GelMA/PEDOT:PSS (0.1% PEDOT:PSS) GelMA/PEDOT:PSS (0.3% PEDOT:PSS) | GelMA |
| Byambaa (2017)                  | succinic anhydride (GelMA−COOH 1/100 mixture) succinic anhydride (GelMA−COOH 1/10 mixture) | GelMA−COOH (1/100) GelMA−COOH (1/10) | GelMA |
| Montesdeoca (2020)              | calcium peroxide (CPO) (0.5 wt %) calcium peroxide (CPO) (1.0 wt %) calcium peroxide (CPO) (3.0 wt %) | GelMA−CPO (0.5%) GelMA−CPO (1.0%) GelMA−CPO (3.0%) | GelMA |
| Bektas (2019)                   | 2-hydroxyethyl methacrylate (HEMA) (GelMA/HEMA (8.2, v/v)) methacrylated alginate (AlgMA) (AlgMA/GelMA = 0.5/4.5) AlgMA (AlgMA/GelMA = 1/4) AlgMA (AlgMA/GelMA = 1.5/3.5) | GelMA−HEMA AlgMA−GelMA (0.5/4.5) GelMA−GelMA (1/4) GelMA−GelMA (1.5/3.5) | GelMA |
| Wei (2015)                      | 15% w/v 150−500 μm bone particle (BP) 15% w/v 0−500 μm BP | 12.5% GelMA +15% 150−500 μm BP 12.5% GelMA +15% 0−500 μm BP | GelMA |
| Camci-Unal (2013)               | 2% (w/v) hyaluronic acid methacrylate (HAMA) 0.5% (w/v) chitosan (CS) | HAMA−GelMA semi-IPN GelMA−CS (0.5%) | GelMA |
| Soo (2018)                      | | | |
Table 2. continued

| the first author (published year) | additives | the experimental group | the control group |
|-----------------------------------|------------|------------------------|------------------|
| Frey (2018)                       | 1% (w/v) chitosan (CS) | semi-IPN GelMA–CS (1%) | 10% GelMA |
| Cross (2018)                      | 2% (w/v) chitosan (CS) | semi-IPN GelMA–CS (2%) | 10% GelMA |
| Liu (2018)                        | 2% (w/v) polyethylene glycol (PEG) | 10% GelMA/2% PEG | 10% GelMA |
| Gu (2020)                         | nanosilicates (nSi) | GelMA–nSi | 5% GelMA |
| Xiao (2020)                       | 2% (w/v) chitosan (CS) semi-IPN GelMA | GelMA–ALNL | 10% GelMA |
| Cross (2018)                      | 2% (w/v) chitosan (CS) semi-IPN GelMA | GelMA–MALNL | 10% GelMA |
| Liu (2018)                        | 2% (w/v) chitosan (CS) semi-IPN GelMA | GelMA–HALNL | 10% GelMA |
| Gu (2020)                         | 1 mg/mL bacterial cellulose (BC) particles | GelMA/BC (1BC) | GelMA |
| Xiao (2020)                       | 1 mg/mL chitosan (CS) semi-IPN GelMA | GelMA/BC (2BC) | GelMA |
| Gu (2020)                         | 4 mg/mL bacterial cellulose (BC) particles | GelMA/BC (4BC) | GelMA |
| Xiao (2020)                       | 8 mg/mL bacterial cellulose (BC) particles | GelMA/BC (8BC) | GelMA |
| Gu (2020)                         | dopamine (DOPA) | GelMA–DOPA | GelMA |
| Xiao (2020)                       | dopamine (DOPA) + melatonin (MT) | GelMA–DOPA@MT | GelMA |
| Jaiswal (2016)                    | 5 mg/mL (Fe) of magnetic nanoparticles (MNPs) | GelMA/MNPs (4 nm) | 5% GelMA |
| Wang (2018)                       | carboxyl-modified mesoporous silica nanoparticles (MSNs-COOH) | MSNs-COOH@gGel | GelMA |
| Suvarnapathaki (2020)             | mesoporous silica nanoparticles (MSNs) | MSNs-NH₂ | 5% GelMA |
| Suvarnapathaki (2020)             | 1 mg/mL hydroxyapatite (HA) | 5G1HA | 5% GelMA |
| Suvarnapathaki (2020)             | 5 mg/mL hydroxyapatite (HA) | 5GSH | 5% GelMA |
| Suvarnapathaki (2020)             | 20 mg/mL hydroxyapatite (HA) | 5G2OH | 5% GelMA |
| Ma (2017)                         | silk microfibers (2.03 ± 0.32 mm) | LF (long fiber + GelMA) | 6% GelMA |
| Garcia-Lizarribar (2018)          | poly(ethylene glycol) dimethacrylate (PEGDA) | GelMA/PEGDA (4/1) | 5% GelMA |
| Garcia-Lizarribar (2018)          | PEGDA (GelMA/PEGDA = 3/2, v/v) | GelMA/PEGDA (3/2) | 5% GelMA |
| Garcia-Lizarribar (2018)          | PEGDA (GelMA/PEGDA = 2/3, v/v) | GelMA/PEGDA (2/3) | 5% GelMA |
| Garcia-Lizarribar (2018)          | PEGDA (GelMA/PEGDA = 1/4) | GelMA/PEGDA (1/4) | 5% GelMA |
| Qiao (2020)                       | osteogenic growth peptide (OGP) | GelMA–OGP | GelMA |

Table 3. Compressive Modulus of the Experimental Group GelMA-Based Composites and the Control Group Pure GelMA of 23 Literatures. Some Literatures Contained Multiple Sets of Data (the Unit of Compressive Modulus is kPa)

| the first author (published year) | group | the mean | the standard deviation | sample size |
|-----------------------------------|-------|----------|------------------------|-------------|
| Shirazi (2016)                    | control group | 3.43 | 1.69 | 3 |
| Moghanian (2020)                  | control group | 3.94 | 4.8 | 3 |
| Moghanian (2020)                  | experimental group 1 | 5.1183 | 32.25 | 4 |
| Serafim (2014)                    | control group | 142.49 | 10.29 | 2 |
| Serafim (2014)                    | experimental group 2 | 757 | 17.75 | 4 |
| Garcia-Lizarribar (2018)          | control group | 142.49 | 10.29 | 2 |
| Garcia-Lizarribar (2018)          | experimental group 1 (AlgMA) | 110.72 | 13.02 | 3 |
| Garcia-Lizarribar (2018)          | experimental group 2 (CMCMA) | 223.76 | 33.06 | 3 |
| Garcia-Lizarribar (2018)          | control group | 5.53 | 2.01 | 3 |
| Garcia-Lizarribar (2018)          | experimental group 1 (AlgMA) | 3.02 | 1.13 | 1 |
| Garcia-Lizarribar (2018)          | experimental group 2 (CMCMA) | 1.96 | 0.16 | 3 |
| Garcia-Lizarribar (2018)          | control group | 3.02 | 1.13 | 1 |
| Garcia-Lizarribar (2018)          | experimental group 3 (PEGDA) | 3.89 | 0.46 | 3 |
| Spencer (2018)                    | control group | 3.02 | 1.13 | 1 |
| Spencer (2018)                    | experimental group 1 (0.1%) | 3.1 | 0.2 | 3 |
| Spencer (2018)                    | control group | 3.6 | 0.1 | 2 |

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Table 3. continued

| the first author (published year) | group | the mean | the standard deviation | sample size |
|---------------------------------|-------|----------|------------------------|-------------|
| Ratheesh (2020) | experimental group 2 (1/4) | 16.14 | 2.50 | 5 |
|  | control group | 4.32 | 1.13 | 2 |
|  | experimental group 3 (1.5/3.5) | 19.55 | 2.60 | 5 |
|  | control group | 4.32 | 1.13 | 2 |
|  | experimental group 1 | 17.40 | 2.39 | 3 |
|  | control group | 14.38 | 1.02 | 2 |
|  | experimental group 2 | 24.83 | 1.02 | 3 |
|  | control group | 14.38 | 1.02 | 2 |
| Camci-Unal (2013) | experimental group | 73.0 | 11.1 | 5 |
|  | control group | 33.6 | 23.2 | 5 |
|  | experimental group 1 (0.5%) | 37.48 | 8.58 | 3 |
|  | control group | 31.08 | 3.61 | 1 |
|  | experimental group 2 (1%) | 49.24 | 4.30 | 3 |
|  | control group | 31.08 | 3.61 | 1 |
|  | experimental group 3 (2%) | 56.59 | 9.15 | 3 |
|  | control group | 31.08 | 3.61 | 1 |
| Suo (2018) | experimental group 1 | 6.41 | 0.67 | 6 |
|  | control group | 3.26 | 0.45 | 6 |
| Frey (2018) | experimental group | 7.5 | 1.7 | 6 |
|  | control group | 6.7 | 0.4 | 6 |
| Liu (2018) | experimental group 1 (LALN) | 0.24 | 0.02 | 5 |
|  | control group | 0.29 | 0.01 | 2 |
|  | experimental group 2 (MALN) | 0.14 | 0.02 | 5 |
|  | control group | 0.29 | 0.01 | 2 |
|  | experimental group 3 (HALN) | 0.11 | 0.01 | 5 |
|  | control group | 0.29 | 0.01 | 2 |
| Gu (2020) | experimental group 1 (1BC) | 208.8 | 33.5 | 3 |
|  | control group | 112.9 | 15.4 | 1 |
|  | experimental group 2 (2BC) | 289.6 | 43.1 | 3 |
|  | control group | 112.9 | 15.4 | 1 |
|  | experimental group 3 (4BC) | 482.8 | 37.1 | 3 |
|  | control group | 112.9 | 15.4 | 1 |
|  | experimental group 4 (8BC) | 811.7 | 23.4 | 3 |
|  | control group | 112.9 | 15.4 | 1 |

2. MATERIALS AND METHODS

2.1. Literature Retrieval. According to the prescribed literature retrieval method of meta-analysis, the retrieval strategies of this paper were as follows: entering the keyword phrases in the databases. The databases retrieved were these: WOS, BIOSIS, CSCD, KJD, MEDLINE, RSCI, and SCIELO. The retrieval keyword phrases are shown in Table 1. The retrieval date was from 1950 to December 17, 2020.

2.2. Literature Screening. The inclusion criteria are as follows: the material studied is the GelMA hydrogel combined with different additives were studied by meta-analysis. This analysis provides a favorable statistical basis for the selection of GelMA with appropriate additives for use in bone tissue engineering framework composite scaffold and bone tissue engineering repair and transplantation.
specific data in the literatures; compressive modulus is obtained by adding different additives. The exclusion criteria are as follows: documents that have been repeatedly included; GelMA precursors were chemically modified before synthesis; there are no specific data about the mean, standard deviation, or sample size in the results.

2.3. Data Extraction. The following data were extracted from the literatures meeting the inclusion criteria: author, year of publication, additives, experimental group, control group, precursors were chemically modified before synthesis; there are no specific data about the mean, standard deviation, or sample size in the results.

Figure 1. Literature screening flow chart.

Figure 2. Forest plot of the meta-analysis of the overall data of 23 literatures. The results of the heterogeneity test were $p < 0.00001$, $I^2 = 99\%$, 95% CI: 3.76–4.46, and the result of test for overall effect was $p < 0.00001$ ($\alpha = 0.05$).

Table:

| Study or Subgroup | Experimental | Control |
|-------------------|-------------|---------|
|                   | Mean        | SD Total | Mean        | SD Total | Weight | Mean Difference | IV Random | 95% CI | Mean Difference | IV Random | 95% CI |
| Ali Nagehi Shreki 2016 | 343±16.9    | 3      | 39.4±3.8    | 3      | 0.0%   | 362.6±(283.72,323.46) |
| Amiri et al. 2016 | 511.8±32.25 | 4      | 142.4±10.29 | 2      | 0.2%   | 369.3±(334.67,404.01) |
| Andrade et al. 2014 | 757±17.75   | 4      | 142.4±10.29 | 2      | 0.2%   | 614.5±(592.02,637.00) |
| Andrade et al. 2014 | 110±72.13   | 3      | 223.7±33.06 | 3      | 0.0%   | -113.5±(-153.25,-72.83) |
| Andrade et al. 2014 | 5.5±3.2     | 1      | 3.2±1.31    | 1      | 0.1%   | 2.5±(0.56,5.66) |
| Andrade et al. 2014 | 1.96±0.18   | 3      | 3.2±1.13    | 1      | 1.8%   | -1.06±(-3.28,1.16) |
| Andrade et al. 2014 | 2.89±0.46   | 3      | 3.2±1.13    | 1      | 1.7%   | 0.93±(-2.41,2.11) |
| Andrade et al. 2014 | 3.1±0.2     | 3      | 3.6±0.12    | 2      | 8.1%   | -0.60±(-1.77,-0.23) |
| Andrade et al. 2014 | 2.7±0.06    | 3      | 3.6±0.12    | 2      | 6.3%   | -0.90±(-1.05,-0.75) |
| Andrade et al. 2014 | 5.9±0.7     | 3      | 6.5±1.2     | 2      | 2.2%   | -0.60±(-2.20,1.00) |
| Andrade et al. 2014 | 5.7±0.6     | 3      | 6.5±1.2     | 2      | 2.8%   | -0.80±(-2.34,0.74) |

Figure 3. Funnel plot of the meta-analysis of the overall data of 23 literatures. The funnel plot of the study was asymmetric, showing that there was publication bias on the compressive modulus among overall 23 literatures.
compressive modulus of pure GelMA hydrogel, and GelMA-based composites. The mean value, standard deviation, and sample size of the compressive modulus were filled into the data extraction table.

2.4. Computing Platform and Test Methods. This meta-analysis was performed using the Review Manager 5.4 software provided by The Cochrane Collaboration. Two test methods were used in this paper: Q test and $I^2$ test.37,38 Q test was used to test the existence and statistical significance of heterogeneity.36 The inspection level of the meta-analysis was $\alpha = 0.05$; that is, for the Q test, when the $p$ value was less than 0.05, the results of different studies were heterogeneous and the heterogeneity was statistically significant; when the $p$ value was greater than 0.05, the heterogeneity was not statistically significant. Meanwhile, $I^2$ test was conducted to evaluate the extent of heterogeneity between different research results, and $I^2$ values of $\leq 25$, >25 and $\leq 50$, >50 and $\leq 75$, and >75% were regarded as indication of no, low, moderate, and high extent of heterogeneity, respectively.38 In the meta-analysis, if the heterogeneity was significant, the random effect model was used; otherwise, the fixed effect model was used.37

3. RESULTS AND DISCUSSION

3.1. Results of Literature Screening and Data Extraction. Through the retrieval strategies in 2.1, a total of 1587 papers were retrieved. After eliminating the repetition and carefully reading the titles and abstracts, 1003 were eliminated because they have no relation to GelMA and its composites, leaving 584. After reading the full text, only 23 literatures finally met the inclusion criteria. The required data were extracted from the 23 included literatures, and the basic information of the included literatures are shown in Table 2.39

Figure 4. Forest plot of the meta-analysis of overall data after processing of 23 literatures. The results of the heterogeneity test were $p < 0.00001$, $I^2 = 100$, 95% CI: 1.24–2.70, and the result of test for overall effect was $p < 0.00001$ ($\alpha = 0.05$).

Figure 5. Funnel plot of the meta-analysis of overall data after processing of 23 literatures. The funnel plot was roughly symmetric without publication bias, showing that there was no publication bias on the compressive modulus among overall data after processing of 23 literatures.
shown in Table 3. The literature screening flow chart is shown in Figure 1.

Twenty-three literatures were obtained through screening, among which, some contained a variety of adding additives and different adding concentrations and proportions. According to the number of literatures, 23 groups of data were obtained. According to the additives, 28 groups of data could be obtained (including the same additives added in different literatures); when different concentrations and proportions of the additives were added, a total of 50 sets of data could be obtained (Tables 2 and 3).

3.2. Results and Discussion of Meta-analysis. 3.2.1. General Analysis. Meta-analysis was conducted on the original data of 23 literatures. Overall, the data analysis forest plot and funnel plot are shown in Figures 2 and 3 respectively. As can be seen from Figure 3, the funnel plot of the study was asymmetric, showing that there was publication bias on the compressive modulus among overall 23 literatures. It can be seen from Figure 2 that the heterogeneity analysis results are $p < 0.00001$, $I^2 = 99\%$, and it can be seen that there was very high heterogeneity among studies and the heterogeneity was statistically significant. Therefore, we adopted the random effect model. According to the overall analysis results, 95% CI: $3.76 - 4.46$, $p < 0.00001$, the difference between the experimental group and the control group was statistically significant.

### Table 3. Type of Photoinitiator Light Exposure Time, Light Intensity, and Concentration of the Photoinitiators Irgacure2959 of the 23 Included Literatures. There Were Some References That Do Not Mention Any of These Items

| the first author (published year, IF) | type of the photoinitiators | light exposure time | light intensity |
|----------------------------------------|-----------------------------|--------------------|-----------------|
| Shirazi (2016, 8.456)                  | 1 mol mL$^{-1}$ Irgacure2959 |                    | 6.9 mW/cm$^2$  |
| Moghanian (2020, 3.319)               | triethanolamine, N-vinyl caprolactam, and eosin Y disodium salt |                | 100 mW/cm$^2$  |
| Serafin (2014, 3.069)                 | 2 mol % Irgacure2959         | 60 min             |                |
| García-Lizarribar (2018, 2.895)       | LAP                         | 5 s                |                |
| Spencer (2018, 4.511)                 | 0.5% (w/v) Irgacure2959      | 200 s              | 1.8 mW/cm$^2$  |
| Byambaa (2017, 6.27)                 | 0.1% (w/v) Irgacure2959      | 20 s               | 6.9 mW/cm$^2$  |
| Montesdeoca (2020, 4.389)             | 0.5% (w/v) Irgacure2959      | 4 min              | 7.7 mW/cm$^2$  |
| Bektas (2019, 2.467)                  | 0.5% (w/v) Irgacure2959      | each side 1 min    | 0.120 J/cm$^2$ |
| Wei (2015, 5.047)                    | 0.5% (w/v) Irgacure2959      |                    |                |
| Ratheesh (2020, 7.367)                | LAP                         | 1 min              | 20 W           |
| Camci-Unal (2013, 5.667)              | 0.1% (w/v) Irgacure2959      |                    |                |
| Suo (2018, 4.959)                    | 0.1% (w/v) Irgacure2959      | 30 s               | 1.5 W/cm$^2$   |
| Frey (2018, 16.836)                  | 0.5% (w/v) Irgacure2959      |                    | 6.9 mW/cm$^2$  |
| Cross (2018, 5.57)                   | 0.25% (w/v) Irgacure2959     | 60 s               | 6.09 mW/cm$^2$ |
| Liu (2018, 3.049)                    | 0.5% (w/v) Irgacure2959      |                    |                |
| Gu (2020, 3.382)                     | LAP                         | 2 min              | 5 W            |
| Xiao (2020, 5.076)                   | 1% (w/v) Irgacure2959        | 10 s               | 6.9 mW/cm$^2$  |
| Jaishwal (2016, 13.903)               | 0.5% (w/v) Irgacure2959      | 60 s               | 30 mW/cm$^2$   |
| Wang (2018, 3.384)                   | 3 mg Irgacure2959           | 1 min              | 30 mW/cm$^2$   |
| Suvarnaphathi 1 (2020, 3.416)        | 0.5% (w/v) Irgacure2959      | 20 s               |                |
| Suvarnaphathi 2 (2020, 3.416)        | 0.5% (w/v) Irgacure2959      | 20 s               |                |
| Suvarnaphathi 3 (2020, 3.416)        | 0.5% (w/v) Irgacure2959      | 30 s               |                |
| Xiao (2018, 2.121)                   | 0.5% (w/v) Irgacure2959      | 60 s               | 7.0 mW/cm$^2$  |
| Ma (2017, 4.511)                     | 2-hydroxy-2-methylpropiophenone | 30 s            | 2.9 mW/cm$^2$  |
| Qiao (2020, 6.267)                   |                             |                    | 30 s           |
The high heterogeneity may be due to the different types of additives, processing techniques, and so forth in each study. In order to solve the problem of heterogeneity and exclude the influence of the above factors, the original data were processed as follows: the new mean of the experimental group = the original mean value of the experimental group/the original mean of the control group; the new standard deviation of the experimental group = the original standard deviation of the experimental group/the original mean value of the experimental group; the new mean of the control group = 1; the new standard deviation of the control group = the original standard deviation of the control group/the original mean of the control group; the processed meta-analysis results are shown in Figures 4 and 5.

After treatment, the funnel plot was roughly symmetric, showing that there was no publication bias on the compressive modulus among the overall data after the processing of 23 literatures. However, $I^2$ was still greater than 75% ($p < 0.00001$, $I^2 = 100$), and the heterogeneity was still large. The difference between the experimental group and the control group was statistically significant (95% CI: 1.24−2.70, $p < 0.00001$); therefore, adding additives to GelMA, making GelMA-based composites, can improve the mechanical properties of the GelMA hydrogel.

### 3.2.2. Data Consolidation

Studies with unclear concentration in the control group were excluded, and the results were analyzed after data combining. The GelMA hydrogel concentration in the control group was divided into three categories: ≥10% (w/v), 5−10% (w/v), and ≤5% (w/v). When the concentration of the control group was ≥10% (w/v) GelMA (Figure 6) ($I^2 = 100$, 95% CI: 0.92−1.77, $p < 0.00001$), there was statistical significance between the experimental group and the control group ($p < 0.00001$). However, as can be seen from Figure 6, the data of Moghanian40 and Serafin41 differed greatly.
from the research data of others. According to the original text, it was found that the type of photoinitiator in Moghanian was different from other studies. As listed in Table 4, the photoinitiator adopted by Moghanian was triethanolamine, N-vinyl caprolactam, and eosin Y disodium salt, which was different from other studies (Irgacure2959 as the photoinitiator). The exposure time of Serafim was 60 min which was much longer than other studies (Table 4). These may be the reasons for the abnormally high numerical values in the two studies. Therefore, we attempted the following: excluding the above two studies, meta-analysis was performed again, and the results are shown in Figure 7. It can be seen from Figure 7 that heterogeneity was still very large, which was $I^2 = 98\%$, and the difference between the experimental group and the control group was statistically significant ($p = 0.006 < 0.05$). Therefore, the additives can improve the mechanical properties of the GelMA hydrogel with the concentration $\geq 10\%$ (w/v), no matter whether there are outliers or not. The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus among GelMA concentration $\geq 10\%$ (w/v) in the control group (Figure 8).

When the concentration of GelMA in the control group was $5$–$10\%$ (w/v) (Figure 9) ($I^2 = 99\%$, 95% CI: $0.98$–$5.60$, $p = 0.005 < 0.05$), the heterogeneity was large, and the difference between the experimental group and the control group was statistically significant, so the additives can improve the mechanical properties of the GelMA hydrogel by $5$–$10\%$ (w/v). The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus among GelMA concentration $\geq 10\%$ (w/v) in the control group (Figure 10).

When the concentration of the control group was $\leq 5\%$ (w/v) GelMA (Figure 11) ($I^2 = 97\%$, 95% CI: $5.29$–$11.09$, $p < 0.00001$), the heterogeneity was large, and the difference between the experimental group and the control group was statistically significant, so the additives could improve the mechanical properties of the GelMA hydrogel with the concentration $\leq 5\%$ (w/v). The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus among GelMA concentration $\leq 5\%$ (w/v) in the control group (Figure 12).

In this study, it is speculated that the asymmetry of funnel plots is mainly caused by publication bias, which is controversial and needs further study.

### 3.2.3. Subgroup Analysis

In the above results, heterogeneity was high and the heterogeneity was statistically significant, so subgroup analysis was used to analyze the sources of heterogeneity.

#### 3.2.3.1. GelMA Concentration in the Control Group

Studies with clear GelMA concentration values in the literatures were selected (Table 2), and they were divided into three groups: $\rho \geq 10\%$ (w/v), $\rho 5$–$10\%$ (w/v), and $\rho \leq 5\%$ (w/v) ($\rho$ is the concentration of GelMA in the control group). The results are shown in Figure 13. As shown in Figure 13, the results of the three subgroups were $I^2 = 91.4\%$, $p < 0.00001$. The three subgroups had high heterogeneity, and the differences among the three subgroups were statistically significant, so GelMA concentration in the control group was one of the sources of heterogeneity. The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus among GelMA concentration $\leq 5\%$ (w/v) in the control group.

#### 3.2.3.2. Type of Photoinitiators

GelMA optical cross-linking must have photoinitiators. The type of photoinitiators, light exposure time, light intensity, and concentration of the photoinitiator Irgacure2959 of the 23 included literatures are shown in Table 4. It can be seen that most of the photoinitiators used in the studies was Irgacure2959, which was the commonly used photoinitiator in GelMA optical cross-linking. Therefore, according to the type of the photoinitiators, the data from 22 literatures explicitly mentioned the type of photoinitiators used were divided into two groups: Irgacure2959 and not Irgacure2959. The results are shown in Figure 15, $I^2 = 99.5\%$, $p < 0.00001$; there was high heterogeneity between the two
groups, and the heterogeneity was statistically significant, so the type of photoinitiators was one of the sources of heterogeneity. The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus of Irgacure2959 and not Irgacure2959 (Figure 16).

3.2.3.3. Light Exposure Time. There were 17 literatures that explicitly mentioned the time used for hydrogel optical cross-linking, so the light exposure time was divided into two groups: \( t \leq 60 \) s and \( t > 60 \) s (\( t \) is the light exposure time). The study of Suvarnapathaki58 included two types of exposure time (Table 4). The exposure time was different according to different added concentrations, but both of them were less than 60 s, so they were recorded as a set of data. The results are shown in Figure 17, \( I^2 = 76.5\% \), \( p = 0.04 < 0.05 \); there was high heterogeneity between the two groups, and the heterogeneity was statistically significant, so light exposure time was one of the sources of heterogeneity. It is worth noting that, differing from other subgroup analysis conditions, when \( t \leq 60 \) s, the funnel plot was basically symmetric, showing that there was no publication bias on the compressive modulus among \( t \leq 60 \) s.
In > 60 s, the funnel plot was asymmetric, showing that there was publication bias on the compressive modulus among > 60 s (Figure 18).

3.2.3.4. Light Intensity. There were 16 literatures that explicitly refer to the light intensity of the experiment, among which units in Bektas,46 Ratheesh,48 and Gu54 cannot be unified with others. So these three articles were excluded, and the remaining 13 articles were divided into two groups according to the light intensity: \( I \leq 10 \text{ mW/cm}^2 \) and \( I > 10 \text{ mW/cm}^2 \) (\( I \) is the light intensity). The results are shown in Figure 19, \( I_2 = 99.2\% \), \( p < 0.00001 \); there was high heterogeneity between the two groups, and the heterogeneity was statistically significant, so light intensity was one of the sources of heterogeneity. The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus of \( I \leq 10 \text{ mW/cm}^2 \) and \( I > 10 \text{ mW/cm}^2 \) (Figure 20).

Figure 15. Forest plot of subgroup analysis of 22 literatures divided into type of photoinitiators as Irgacure2959 and not Irgacure2959. In Irgacure2959, the results of the heterogeneity test were \( p < 0.00001 \), \( I^2 = 99\% \), and the result of test for overall effect was \( p < 0.00001 \). In not Irgacure2959, the results of the heterogeneity test were \( p < 0.00001 \), \( I^2 = 100\% \), and the result of test for overall effect was \( p < 0.00001 \). Then, the results of test for subgroup differences were \( p < 0.00001 \), \( I^2 = 99.5\% \) (\( \alpha = 0.05 \)).

Figure 16. Funnel plot of subgroup analysis of 22 literatures divided into type of photoinitiators as Irgacure2959 and not Irgacure2959. The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus of Irgacure2959 and not Irgacure2959.
sources of heterogeneity. The photoinitiator used in most of the studies was Irgacure2959, and it has been clearly shown in the literature that the concentration of the photoinitiator has an effect on the mechanical properties of GelMA. Therefore, we analyzed the concentration of the photoinitiator Irgacure2959 as a subgroup. There were 17 literatures which used Irgacure2959 as the photoinitiator; herein, the units of Shirazi, Serafi, and Wang could not be unified with others. Finally, 14 literatures were divided into two groups: $\rho_I \geq 0.5%$ (w/v) and $\rho_I < 0.5%$ (w/v) ($\rho_I$ is the concentration of the photoinitiator Irgacure2959). The results are shown in Figure 21, $I^2 = 75.3\%$, $p = 0.04 < 0.05$; there was high heterogeneity between the two groups, it was close to the moderate extent heterogeneity ($\leq 75\%$), and the heterogeneity was statistically significant, so the concentration of the photoinitiator Irgacure2959 was one of the sources of heterogeneity. The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus of $\rho_I \geq 0.5%$ (w/v) and $\rho_I < 0.5%$ (w/v) (Figure 22).

3.3. Discussion. For the GelMA hydrogel, the types and amounts of additives are the sources of heterogeneity among studies. The mechanical properties of the GelMA hydrogel are different due to the different types and doses of additives. The mechanical properties of the GelMA hydrogel can be affected by changes in its shape, even with the same additives, so a variety of double-network and fibrous structures have emerged.

Figure 17. Forest plot of subgroup analysis of 17 literatures divided into light exposure time as $t \leq 60$ s and $t > 60$ s ($t$ is the light exposure time). In $t \leq 60$ s, the results of the heterogeneity test were $p < 0.0001$, $I^2 = 99\%$, and the result of test for overall effect was $p = 0.0001$. In $t > 60$ s, the results of the heterogeneity test were $p < 0.0001$, $I^2 = 99\%$, and the result of test for overall effect was $p = 0.0001$. Then, the results of the test for subgroup differences were $p = 0.04$, $I^2 = 76.5\%$ ($\alpha = 0.05$).

Figure 18. Funnel plot of subgroup analysis of 17 literatures divided into light exposure time as $t \leq 60$ s and $t > 60$ s ($t$ is the light exposure time). Specially, in $t \leq 60$ s, the funnel plot was basically symmetric, showing that there was no publication bias on the compressive modulus among $t \leq 60$ s. In $t > 60$ s, the funnel plot was asymmetric, showing that there was publication bias on the compressive modulus among $t > 60$ s.
As mentioned in Wang’s article, incorporating NPs, CNTs, and graphene oxide into the GelMA hydrogel, there was no significantly observed increases in the compressive modulus; these NPs did not obviously increase the mechanical stiffness of the hydrogel network because they simply acted as physical fillers. Nevertheless, the chemical cross-linking of modified NPs to polymer chains can significantly increase the stiffness. In addition, a large number of literatures have shown that the differences of preparation methods in various studies also lead to changes in mechanical properties, such as GelMA concentration, photoinitiator concentration, MA concentration, cooling rate, UV dose, temperature gradient, and so forth. These reasons were manifested as excessive heterogeneity or become the main sources of heterogeneity in the meta-analysis.

In this paper, a systematic and comprehensive analysis was conducted on whether the mechanical properties of the GelMA hydrogel could be improved by adding additives. This is of great significance for limited application of GelMA in bone tissue engineering scaffold due to its poor mechanical properties. It is also applicable to other applications that are limited by the poor mechanical properties of GelMA. Comprehensive basis and consideration are provided for others to select suitable additives to improve the mechanical properties of the GelMA hydrogel.

This paper listed the selected additives of the articles included and also included the type of photoinitiators used, the light exposure time, the light intensity, the concentration of the photoinitiator Irgacure2959, and the concrete values of the compressive modulus of the GelMA-based composites and the pure GelMA hydrogel. These provide reference standard and inspiration to create new composites. In this analysis, most of the data results showed that there was publication bias on the compressive modulus among the studies, indicating that the results were not consistent and uniform, which was controversial and needs more research. Many literatures were not included in this study because of the lack of specific values of the compressive modulus or others, and the results of this paper showed there was a certain publication bias, so this paper needs to be improved with more articles and data in the future.

4. CONCLUSIONS

Meta-analysis was adopted to evaluate the influence of additives on the compressive modulus of GelMA-based composites.
The results showed that there was publication bias among the data from the 23 papers. After corresponding data processing, there was no publication bias. The data were analyzed and combined to obtain the following consequences: the concentration of GelMA was ≤5% (w/v), 5%−10% (w/v), and ≥10% (w/v) in the control group, and the additives could improve the mechanical properties of GelMA. Through subgroup analysis, it can be inferred that the GelMA hydrogel concentration in the control group, the type of photoinitiators, the time of light exposure, the intensity of light exposure, and the concentration of the photoinitiator Irgacure2959 were all sources of heterogeneity.

Figure 21. Forest plot of subgroup analysis of 14 literatures divided into the concentration of the photoinitiator Irgacure2959 as ρI ≥ 0.5% (w/v) and ρI < 0.5% (w/v) (ρI is the concentration of the photoinitiator Irgacure2959). In ρI ≥ 0.5% (w/v), the results of the heterogeneity test were p < 0.00001, I² = 99%, and the result of test for overall effect was p < 0.00001. In ρI < 0.5% (w/v), the results of the heterogeneity test were p < 0.00001, I² = 87%, and the result of test for overall effect was p = 0.01. Then, the results of test for subgroup differences were p = 0.04, I² = 75.3% (α = 0.05).

Figure 22. Funnel plot of subgroup analysis of 14 literatures divided into the concentration of the photoinitiator Irgacure2959 as ρI ≥ 0.5% (w/v) and ρI < 0.5% (w/v) (ρI is the concentration of the photoinitiator Irgacure2959). The funnel plot was asymmetric, showing that there was publication bias on the compressive modulus of ρI ≥ 0.5% (w/v) and ρI < 0.5% (w/v).

The authors declare no competing financial interest.
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